Renal fibrosis assessment by diffusion-weighted magnetic resonance Imaging

FRIEDLI, Iris

Abstract

The goal of this PhD was to improve kidney fibrosis assessment by diffusion-weighted imaging (DWI). A respiratory implementation of the RESOLVE sequence improved significantly the image quality by reducing susceptibility effects and enhancing cortico-medullary Apparent Diffusion Coefficient (ADC) differentiation. In light of that fact, RESOLVE was tested in well-controlled models of fibrosis to separate pathological from healthy kidneys. These results were validated afterward in a cohort of kidney allograft patients. ∆ADC from RESOLVE had a stronger correlation to fibrosis than ∆ADC from classical single-shot Echo-Planar DWI. Most importantly, a negative ∆ADC was measured for all patients harboring more than 40% fibrosis, opening the possibility for a diagnostic threshold. In a second part, a motion compensation method was provided to remove signal dropout and the overestimation of ADC. By addressing and minimizing the main sources of the initial poor DW image quality, it was possible to improve renal fibrosis assessment.

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Renal Fibrosis Assessment by Diffusion-Weighted Magnetic Resonance Imaging

THÈSE

présentée à la Faculté des sciences de l’Université de Genève
pour obtenir le grade de Docteur ès sciences, mention Physique

par
Iris FRIEDLI

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Genève, le 30 octobre 2017

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Publications included in PhD thesis


4. **Friedli I, Crowe LA, Delattre B MA, de Perrot T, Martin PY, de Seigneux S, Vallée JP.** The Cortico-Medullary ADC Difference Reduces Inter-System Variability in Renal Diffusion-Weighted Imaging. In preparation


Other Publications not-included in PhD thesis


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**List of abbreviations**

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<th>Abbreviation</th>
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<td>ADC</td>
<td>Apparent Diffusion Coefficient</td>
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<tr>
<td>ANOVA</td>
<td>One-way analysis of variance</td>
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<td>AUCs</td>
<td>Area Under the Curves</td>
</tr>
<tr>
<td>BSA</td>
<td>Bovine Serum Albumin</td>
</tr>
<tr>
<td>DDC</td>
<td>Distributed Diffusion Coefficient</td>
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<tr>
<td>CKD</td>
<td>Chronic Kidney Disease</td>
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<tr>
<td>CV</td>
<td>Coefficient of Variation</td>
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<td>DKI</td>
<td>Diffusion Kurtosis Imaging</td>
</tr>
<tr>
<td>DSA</td>
<td>Donor Specific Antibodies</td>
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<tr>
<td>DTI</td>
<td>Diffusion Tensor Imaging</td>
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<tr>
<td>DWI</td>
<td>Diffusion-Weighted Imaging</td>
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<tr>
<td>eGFR</td>
<td>estimated Glomerular Filtration Rate</td>
</tr>
<tr>
<td>EPI</td>
<td>Echo-Planar Imaging</td>
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<tr>
<td>ES</td>
<td>Echo Spacing</td>
</tr>
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<td>ETL</td>
<td>Echo Train Length</td>
</tr>
<tr>
<td>FA</td>
<td>Fractional Anisotropy</td>
</tr>
<tr>
<td>FOV</td>
<td>Field Of View</td>
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<tr>
<td>GRAPPA</td>
<td>GeneRalized Autocalibrating Partially Parallel Acquisitions</td>
</tr>
<tr>
<td>GRE</td>
<td>GRadient Echo</td>
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<tr>
<td>HASTE</td>
<td>Half-Fourier single-shot spin echo</td>
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<td>IF</td>
<td>Interstitial Fibrosis</td>
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<tr>
<td>IVIM</td>
<td>Intravoxel Incoherent Motion</td>
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<tr>
<td>KARs</td>
<td>Kidney Allograft Recipients</td>
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<tr>
<td>MLR</td>
<td>Multiple Linear Regression</td>
</tr>
<tr>
<td>MOLLI</td>
<td>Modified Look-Locker Inversion Recovery</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<tr>
<td>NFS</td>
<td>Nephrogenic Systemic Fibrosis</td>
</tr>
<tr>
<td>PACE</td>
<td>prospective acquisition correction technique</td>
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<td>PE</td>
<td>Phase-encoding</td>
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<tr>
<td>PMCMR</td>
<td>Pairwise Multiple Comparisons of Mean Rank Sums</td>
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<tr>
<td>RESOLVE</td>
<td>REadout Segmentation Of Long Variable Echo Train</td>
</tr>
<tr>
<td>rf</td>
<td>radiofrequency</td>
</tr>
<tr>
<td>RMSE</td>
<td>Root Mean Squared Error</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver Operating Characterisitic</td>
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<tr>
<td>ROI</td>
<td>Region Of Interest</td>
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<tr>
<td>SE</td>
<td>Spin Echo</td>
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<tr>
<td>SENSE</td>
<td>SENSitivity Encoding</td>
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<tr>
<td>SI</td>
<td>Signal Intensity</td>
</tr>
<tr>
<td>TA</td>
<td>Acquisition time</td>
</tr>
<tr>
<td>TE</td>
<td>Echo Time</td>
</tr>
<tr>
<td>TMIP</td>
<td>Temporal Maximum Intensity Projection</td>
</tr>
<tr>
<td>TR</td>
<td>Repetition time</td>
</tr>
<tr>
<td>USPIO</td>
<td>Ultra Small Superparamagnetic Iron Oxide Nanoparticle</td>
</tr>
<tr>
<td>UUO</td>
<td>Unilateral Ureteral Obstruction</td>
</tr>
<tr>
<td>WIP</td>
<td>Work In Progress</td>
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Abstract

Chronic kidney disease (CKD) is a significant worldwide health problem, with an incidence of 10% in Switzerland. Apparition and progression of fibrosis in the kidney tubulo-interstitial space is highly predictive of CKD evolution. Currently, renal fibrosis is estimated by biopsy. This procedure suffers from multiple limitations, such as sampling effect and significant risk of complications (bleeding or infection). Based on this clinical feedback, a need exists to noninvasively assess kidney interstitial fibrosis.

Magnetic resonance imaging (MRI) allows the acquisition of diffusion-weighted imaging (DWI), sensitive to water motion within tissue. Recent studies have shown a decrease of the Apparent Diffusion Coefficient (ADC) from DWI with an increase of interstitial fibrosis, probably due to collagen accumulation in the interstitium. The hope is that renal DWI could limit the number of "unnecessary" biopsies in CKD patients. However, renal DW image quality is suboptimal due to susceptibility and motion artifacts. Indeed, the particularity of the kidney is its inherent motion and its proximity to the air-filled intestine. The consequent ADC variability between studies prevents definition of abnormal ADC values suitable for a diagnostic threshold. More importantly, ADC variability occurs also in healthy volunteers without known renal dysfunction, which limits the possibility of recognized reference values for healthy kidney ADC. Therefore, the goal of this PhD was to provide practical solutions to improve kidney fibrosis assessment by MRI. In particular, this work addresses the challenge of improving renal DW image quality by reducing susceptibility artifacts (blurring, distortion) and motion effects. Resolution of these problems would reduce ADC variability and enable a non-invasive fibrosis assessment tool. This is of obvious benefit to the patient over the current standard of care, which is repeated biopsy. An important effort was devoted to validate a DWI protocol in phantoms, small animal models and healthy volunteers before it was applied in a cohort of CKD patients.

To this aim, I addressed three major open issues. In a first step, an important part of this PhD thesis concerned the optimization of the MR protocol acquisition. A respiratory implementation of a REadout Segmentation Of Long Variable Echo train (RESOLVE) sequence improved significantly the quality of renal DWI by reducing susceptibility effects, increasing sharpness and enhancing cortico-medullary differentiation. This enabled measurement of the ADC difference between the cortex and medulla (ΔADC) (first publication of this PhD work). In light of that fact, RESOLVE was tested in a preclinical study to differentiate different levels of interstitial fibrosis and inflammation in well-controlled small animal models. It was possible to separate, with DWI on a clinical MR system, pathological from healthy kidneys in moderate and severe experimental models of fibrosis. These results were validated afterward in a small homogeneous cohort of 29 kidney allograft patients (second publication of this thesis). A strong correlation was measured between ΔADC and the biopsy specimen fibrosis quantification in our cohort of kidney allograft patients, whereas the correlation of ΔADC to kidney inflammation was weak. ΔADC from RESOLVE had a stronger correlation to the percentage of fibrosis outperforming both ΔADC from classical single-shot Echo-Planar Imaging (third publication) as well as the cortico-medullary difference of spin-lattice relaxation time (ΔT1). Most importantly, a negative ΔADC value was measured for all patients harboring more than 40% interstitial fibrosis, opening the possibility for a diagnostic threshold. However, ADC variability persisted between patients with the same percentage fibrosis. This variability could arise from different sources, and the exact cause is still undetermined. In a further study (publication in preparation), ADC reproducibility between five MR systems (Siemens and Philips, 1.5T and 3T) was investigated in healthy volunteers. In that experiment, ADC variability could not be explained purely by the difference in MR system, but it is certainly link to physiology, since the ADC variation was below 5% in a phantom. In healthy volunteers, the use of the ΔADC allowed reduction of ADC variations between MR systems, compared to cortical and medullary ADC separately. In addition, in our studies, where small regional variations of ADC are investigated, any motional signal intensity dropout needs to be eliminated. This PhD work also addressed the variability due to motion, currently lacking in the literature (publication in preparation). Despite the use of a prospective respiratory navigator in the acquisition scheme, residual motion degraded kidney DW image quality. A mean of 10%, up to a maximum of 44% signal intensity variation was observed between consecutive slices. A motion compensation method, based on Temporal Maximum Intensity Projections, was provided to overcome this
problem. This step was important to remove signal dropout, which would lead to an overestimation of ADC values. By addressing the initial poor DW image quality and minimizing the main sources of variability and pitfalls, it is possible to significantly improve renal fibrosis assessment.

In conclusion, this thesis investigates the feasibility of measuring kidney interstitial fibrosis more reliably by taking into account kidney particularities. Thereby, all results presented in this thesis work may serve as a basis to optimize future renal DWI.
Résumé


Pour évaluer la fibrose rénale de manière non-invasive, nous étudions l’imagerie de diffusion par résonance magnétique comme alternative à certaines biopsies de routine faite chez les patients MRC. Cependant, la qualité habituelle des images de diffusion rénale est sous-optimal et souffre de nombreux artefacts. En effet, en raison de sa position dans l’abdomen, le rein est sujet aux artefacts de mouvement et de susceptibilité magnétique, notamment à cause de sa proximité avec les intestins pouvant contenir de l’air. La conséquence directe est une variabilité des valeurs de CAD, empêchant la définition de valeurs "anormales", nécessaire à l’établissement d’un seuil diagnostique. Plus important encore, la variabilité des valeurs de CAD est également présente chez des volontaires sains (sans pathologie connue des reins) ce qui limite la possibilité de valeurs de référence.

Dans cette thèse, nous étudions des solutions pratiques pour améliorer l’évaluation de la fibrose rénale par IRM, notamment, en réduisant les artefacts de susceptibilité et de mouvements présent en imagerie de diffusion. En minimisant ces problèmes, nous cherchons à réduire la variabilité du CAD pour en augmenter la fiabilité diagnostique. Un protocole d’imagerie a été validé en utilisant successivement différents fantômes de test, des petits animaux modèles puis des volontaires sains, avant que ce protocole ne soit appliqué dans une cohorte de patients MRC.

La première partie de cette recherche concerne l’optimisation du protocole d’acquisition. L’implémentation d’une séquence RESOLVE (REadout Segmentation Of Long Variable Echo Train) a amélioré de manière significative la qualité des images de diffusion rénale en réduisant les effets de susceptibilité, en augmentant la netteté et la différenciation cortico-médullaire. Cela nous a permis de mesurer une différence de CAD entre le cortex et la médulla (ΔCAD) (première publication dans ce travail de thèse). La séquence RESOLVE a été testée dans une étude préclinique pour différencier les degrés de fibrose et d’inflammation dans un modèle de fibrose sévère et modéré. Grace à cette méthode, il a été possible de différencier chez les petits animaux les reins pathologiques des reins sains, en utilisant un IRM clinique. Ces résultats encourageants ont été validés, dans un deuxième temps, avec une petite cohorte homogène de 29 patients MRC qui a aboutit à la deuxième publication dans ce travail de thèse. Une corrélation significative a été mesurée entre le ΔCAD et le taux de fibrose dans notre cohorte, tandis que la corrélation entre le ΔCAD et le taux d’inflammation était faible. La corrélation entre le ΔCAD obtenu avec la séquence RESOLVE et la fibrose était plus importante que celles obtenues avec le ΔCAD de la séquence single-shot Echo-Planar Imaging (séquence habituellement utilisée en diffusion rénale), ainsi qu’avec la différence cortico-médullaire du temps de relaxation (ΔT1). Plus important encore, un ΔCAD négatif a été mesuré chez l’ensemble des patients ayant un taux de fibrose interstitiel supérieur à 40%, ouvrant la possibilité d’un seuil diagnostique. Cependant, une variabilité persistait sur le CAD des patients ayant le même taux de fibrose. Cette variabilité peut provenir de différentes sources et, sa cause exacte est à l’heure actuelle toujours méconnue.

Dans une étude en cours, la reproductibilité du CAD entre différents systèmes IRM (Siemens et Philips à 1.5T et 3T) a été investigué chez des volontaires sains. Dans cette expérience, la variabilité du CAD ne
peut pas être purement expliqué par les différences entre les machines, puisque moins de 5% de différences ont été mesuré sur un fantôme de test. L'utilisation du ΔCAD chez les volontaires sains permettait de réduire les variations de CAD, en comparaison avec le CAD du cortex et de la médulla analysés séparément.

Dans cette étude ou de faibles variations de CAD sont recherchées, toute perte d’intensité de signal dû aux mouvements est préjudiciable à l’analyse et devrait être minimisé (publication en préparation). En dépit de l’utilisation d’un navigateur au cours de l’acquisition, la présence de mouvements résiduels dégradait la qualité des images de diffusion rénale. Une moyenne de 10% de variabilité a été mesurée sur les variations d’intensité de signal avec des maximums pouvant atteindre 44% entre des coupes consécutives. Une méthode de compensation de mouvement a été mise en place pour compenser les pertes de signal observées lors de la diffusion rénale. Cette étape était importante pour éliminer les pertes de signal, qui ont pour conséquence une surestimation du CAD. En répondant au problème initial de mauvaise qualité de l’image et en minimisant les principales sources de variabilité, il a été possible d’améliorer de manière significative l’évaluation de la fibrose rénale.

En conclusion, cette thèse investigue la faisabilité de mesurer la fibrose interstitielle du rein de manière plus fiable et moins invasive par IRM en prenant en compte les particularités du rein.
1 Introduction

The overarching research theme of this PhD thesis was to assess renal interstitial fibrosis, based on Magnetic Resonance Imaging (MRI). MRI is a non-invasive imaging modality, which is sensitive to a wide range of contrast mechanisms including Diffusion-Weighted Magnetic Resonance Imaging (DW-MRI or DWI). DWI has an important role to play in kidney physiopathology assessment, making it an emerging imaging modality for renal fibrosis quantification. Most of this thesis was focused on DWI by addressing the fundamental problems encountered in the case of renal application.

The following introductory chapter is divided into two main parts. The first part provides an overview of the basic principles involved in DWI required for the subsequent chapters. The second part of this introduction is dedicated to the current issues affecting renal DWI.

1.1 Physical background behind DWI

1.1.1 Brownian motion

Robert Brown wondered about the phenomenon of random motion, while he observed through his microscope pollen grains, constantly in random motion due to their intrinsic thermal energy [6]. Brownian motion describes an ensemble of particles moving randomly in space, colliding with each other and bouncing back and forth. On the microscopic level, at any time step, the particle moves over a random displacement, also known as random walk process \( \{X_n : n \geq 0\} \). If the particle position at time zero is \( X_0 \), its position at time \( n \) will be given by:

\[
X_n = X_0 + \sum_{i=1}^{n} \sum_{j=1}^{n} (\epsilon_i \cdot \epsilon_j) \cdot x_i \tag{1}
\]

\[
X_n = X_0 + \sum_{i=1}^{n} \epsilon_i^2 \cdot x_i \tag{2}
\]

The random number \( \epsilon = \pm 1 \) is defined such as \( \langle \epsilon_i \cdot \epsilon_j \rangle = 0 \) if \( i \neq j \) or \( \langle \epsilon_i \cdot \epsilon_j \rangle = 1 \) if \( i=j \), and \( x_i \) \( (i=1, \ldots N) \) are assumed to be independent, identically distributed random variables with values in \( \mathbb{R}^d \).

Diffusion can be considered as a macroscopic manifestation of Brownian motion on the microscopic level. The theory connecting the diffusion phenomenon to temperature and properties of the medium and particles was provided by Albert Einstein [19]. Albert Einstein established that molecules could travel in space over a distance that is statistically well described by a diffusion coefficient \( D \) according to:

\[
D = \frac{k_B T}{6\pi \eta r} \tag{3}
\]

The diffusion coefficient \( D \) depends only on the Boltzmann’s constant \( k_B = 1.38 \times 10^{-23} \text{ J/K} \), the media temperature \( T \), the coefficient of viscosity of the liquid \( \eta \) and the radius of the particle \( r \).

The average squared displacement of particles, \( \langle \Delta r^2 \rangle \) that are allowed to diffuse freely in 3 dimensions, is given by:

\[
\langle \Delta r^2 \rangle = \langle |X(t + x) - X(t)|^2 \rangle \tag{4}
\]

\[
= 6D\Delta t \tag{5}
\]

\( \langle \Delta r^2 \rangle \) is proportional to the interval in time \( \Delta t \) for which particles are allowed to diffuse freely. The free water diffusion coefficient (free mobility under unhindered conditions) at 37°C is about \( 3000 \times 10^{-6} \text{ mm}^2/\text{s} \) in an "infinite isotrope medium" i.e. in an infinite medium in which physical properties do not depend on the orientation. At this temperature, 68% of water molecules could explore a circle of 17 \( \mu \text{m} \) radius in 50 ms, whereas only 5% exceeded 34 \( \mu \text{m} \).
The statistical evaluation of Brownian motion, and more generally of the stochastic process, relies on the central limit theorem. Brownian motion is composed of a sequence of normally distributed random displacements. An example of the Brownian motion, with one and two dimensional displacements of a single particle, was simulated and shown in Figure 1.

![Simulation of the Brownian motion of a single particle in two dimensions.](image)

Figure 1: Simulation of the Brownian motion of a single particle in two dimensions. The histogram plots the distribution of the random generated displacements (particle trajectory in 1D). Extending this to 2D gives the second graph. The displacement squared is plotted against the theoretical value of displacement squared (pink line). As shown in equation 5, displacement squared is expected to increase linearly with $\Delta t$.

### 1.1.2 Concept of DW-MRI

DWI is an MRI technique that probes the motion of the abundant water molecules in biological tissues. The diffusion in tissues cannot be considered as completely free on a long timescale, and it is precisely the diffusion pattern that gives microscopic information about tissue architecture. The water molecule displacement depends of the compartment (intravascular, interstitial, intracellular space) in which the molecules are located. The extracellular water diffusion is currently the main object of exploration in DWI.

- "Extracellular" water refers to water "outside" the cell and is considered as unrestricted. However, water molecules are in constant interaction with tissue components, such as cell membranes, fibers and macromolecules [47], which lead to "hindrance" to the free mobility of water.

- "Intracellular" is used in opposition to "extracellular" and refers to water "inside" the cell. Intracellular water is considered as restricted diffusion due to the confinement by cell membrane (if cell boundary is impermeable to water) [13, 11].

Typically, because of hardware limitations, clinical MR probes only unrestricted diffusion. The first human DWI were obtained by Le Bihan et al. [48] in 1985 on a 0.5T MR system. Le Bihan et al. introduced at that time the notion of Intravoxel Incoherent Motion (IVIM) for microscopic translational motion. The initial goal of Le Bihan was to obtain images of brain function, based on the idea that DWI could also be made
sensitive to blood flow through the IVIM concept.

The first major success of DWI came from the early diagnosis of cellular homeostasis alterations in acute cerebral ischemia [56]. DWI was able to detect ischemic lesions in the acute phase, within the optimum time for medical care, long before detection of brain lesions by traditional $T_2$-weighted imaging.

1.1.3 Relaxation phenomenon with diffusion term

In this subsection, the diffusion phenomenon is revisited in the framework of the Bloch differential equations, which describe the magnetization time evolution in the presence of a magnetic field. The interested reader can find more detailed information in reference [81, 32]. The Bloch equations incorporate the relaxation times $T_1$ and $T_2$ that provide the most basic intrinsic contrast mechanism in MR images. In DWI, we are interested for the first description of the spin echo sequence, also first reported the self-diffusion phenomenon (1950) [33]. He noticed that signal is not only attenuated by the influence of dephasing due to translational moving spins. The additional dephasing of moving spin lead to a faster decay of the signal than anticipated. In 1956, Henry Cutler Torrey proposed, a generalization of the Bloch equations which incorporates effects due to the diffusion of magnetization [81]. The Bloch-Torrey equations for the first time evolution in the presence of a magnetic field. The interested reader can find more detailed information in reference [81, 32]. The Bloch equations incorporate the relaxation times $T_1$ and $T_2$ that provide the most basic intrinsic contrast mechanism in MR images. In DWI, we are interested for the first description of the spin echo sequence, also first reported the self-diffusion phenomenon (1950) [33]. He noticed that signal is not only attenuated by the influence of dephasing due to translational moving spins. The additional dephasing of moving spin lead to a faster decay of the signal than anticipated. In 1956, Henry Cutler Torrey proposed, a generalization of the Bloch equations which incorporates effects due to the diffusion of magnetization [81]. The Bloch-Torrey equations were originally defined as follow:

\[
\frac{\partial M_x}{\partial t} = \gamma (M \times H)_x - \frac{M_x}{T_2} + \nabla . D \nabla (M_x - M_{x0}) \tag{6}
\]

\[
\frac{\partial M_y}{\partial t} = \gamma (M \times H)_y - \frac{M_y}{T_2} + \nabla . D \nabla (M_y - M_{y0}) \tag{7}
\]

\[
\frac{\partial M_z}{\partial t} = \gamma (M \times H)_z - \frac{(M_0 - M_z)}{T_1} + \nabla . D \nabla (M_z - M_{z0}) \tag{8}
\]

$\vec{M}$ is the spin magnetization (the resultant sum of all angular momentum vectors) in the magnetic field, $\gamma$ the gyromagnetic ratio specific for a given nucleus (for water protons: $\gamma = 2.68 \times 10^8$ rad/s.T), $H$ is proportional to the static magnetic field $B$, $M_{x,y,z}$ are the components of the magnetization in the $x$, $y$, $z$ directions, $M_0$ is the magnetization at thermal equilibrium, and $D$ is the diffusion coefficient. The ‘drift’ terms $M_{x0}, M_{y0}, M_{z0}$ are in general small and their effects almost always negligible. $T_1$ and $T_2$ are the longitudinal and transverse sample specific relaxation times:

- $T_1$ is the longitudinal relaxation time i.e. the time constant that characterizes the return to equilibrium of the net magnetization along the direction of the static magnetic field $B_0$. $T_1$ is also called the spin-lattice relaxation time.
- $T_2$ is the transverse relaxation time i.e. the characteristic time for loss of phase coherence of a cluster of spins. $T_2$ is the time constant that characterizes the spin-spin decay of the transverse magnetization.

The relaxation terms $T_1$ and $T_2$ can be neglected in the simplified Bloch-Torrey equation such as:

\[
\frac{\partial \vec{M} (\vec{r}, t)}{\partial t} = \gamma \vec{M} (\vec{r}, t) \times \vec{B} + D \nabla^2 \vec{M} (\vec{r}, t) \tag{9}
\]

with $\vec{B} \equiv \vec{G} \cdot \vec{r} \times \vec{r}$.

The magnetization in the transverse plane $M_{xy}(\vec{r}, t) = M_x(\vec{r}, t) + i M_y(\vec{r}, t)$ is such that:

\[
\frac{\partial M_{xy}(\vec{r}, t)}{\partial t} = -i \gamma (\vec{r} \cdot \vec{G}) M_{xy}(\vec{r}, t) + D \nabla^2 M_{xy}(\vec{r}, t) \tag{10}
\]

For $D=0$, the solution of the Bloch-Torrey equation is:

\[
M_{xy}(\vec{r}, t) = A e^{-i \gamma \vec{r} \cdot \vec{G}(\vec{r}) dt} \tag{11}
\]
with $A$ a function of the signal attenuation, depending of $t$ only. This is equivalent to a spatially invariant diffusion effect.

For $D \neq 0$:

$$\frac{\partial A(t)}{\partial t} = e^{i\gamma \cdot \tau} \cdot \int_0^t G(t')dt' D \nabla^2 M_{x,y}(\vec{r}, t) \quad (12)$$

### 1.1.4 Signal detection

MR signal comes from the detection of the electromotive force $(emf)$ generated in a radiofrequency coil by the time-varying magnetic field of precessing magnetization. In practice, an MRI sequence starts by tipping the magnetization vector $\vec{M}$ away from its alignment along the static magnetic field $\vec{B}_0$ ($\vec{B}_0=[0 \ 0 \ B_0]^T$) by the application of a radiofrequency field $B_1$ (rf pulse) set at the Larmor frequency. After the rf pulse has been turned off, the magnetization vector starts to return to equilibrium i.e. to realign with the static magnetic field $\vec{B}_0$ without stopping its precession. The flux through the coil $\Phi_M$ depends on the spin density, and according to the Faraday’s law of electromagnetic induction:

$$emf = -\frac{d}{dt} \Phi_M(t) \quad (13)$$

$$= -\frac{d}{dt} \int_{\text{sample}} d^3 r \vec{M}(\vec{r}, t) \cdot \vec{B}^{\text{receive}}(\vec{r}) \quad (14)$$

with $\vec{B}^{\text{receive}}$ the ‘receive’ field produced by the coil.

Once the MR signal has been created, a spatial encoding of the signal is necessary to form an image. The signal intensity can be determined as a function of frequency through the Fourier transformation. The precessional frequency $f$ at position $z$ is given by:

$$f(z) = f_0 + \frac{\gamma}{2\pi} G_z z \quad (15)$$

with $f_0 = \frac{\gamma}{2\pi} B_0$ the Larmor precession frequency at $z=0$.

A gradient, created by electromagnetic gradient coils inside the magnet, is superposed on the main magnetic field to cause a position-dependent phase and frequency shift. With the application of the gradient, the strength of the MR signal, at each frequency, gives a measure of the signal strength at each position. The domain of spatial frequency of the signal is referred to as the k-space. k-space contains the raw MR data. The spatial frequency $k(t)$ is given by:

$$k(t) = \frac{\gamma}{2\pi} \int_0^t G(t')dt' \quad (16)$$

Every point in the k-space contains part of the information for the complete image. Data acquired near the origin of k space contain low frequency components of the image i.e. contrast of the image. Whereas, the details of the image, i.e. information regarding the edges and the contours of the image, are encoded into the high frequencies. An illustration of the effect of nulling chosen regions of the k-space from a full k-space matrix is shown in Figure 2.
A variety of patterns have been proposed to sample the full k-space. We are focusing on Cartesian sampling (in particular the Echo-Planar Imaging (EPI) strategy), which is the strategy most widely used in clinical routine for DWI. In conventional cartesian imaging, k-space is sampled line-by-line. A gradient along the phase encoding axis is applied during signal acquisition, followed by a gradient along the frequency encoding axis, also called readout. The repetition time (TR) corresponds to the time needed to acquire one readout line of k-space after an rf pulse. This process is repeated until desired resolution is achieved along phase direction. The acquisition time (TA) is given by:

$$TA = TR \times N_{PE}$$

(17)

with $N_{PE}$ is the number of phase-encoding lines in the k phase direction.
EPI strategy:

EPI was developed to fill the full k-space faster and counteract the long acquisition time of the conventional cartesian strategy. In 1977, when Peter Mansfield suggested the EPI strategy, it took typically the order of one hour to acquire one conventional image. EPI is much faster than conventional strategy and reduces time needed to acquire an image to milliseconds. An illustration of the single-shot EPI and readout-segmented EPI, compared to the conventional cartesien line-by-line acquisition strategy is shown in Figure 3.

- In single-shot EPI, all k-space lines that form an image are acquired after a single rf excitation pulse using an alternating gradient along the readout trajectory to generate gradients echoes. The total number of echoes is defined as the Echo Train Length (ETL), and the space between echoes is defined as the Echo Spacing (ES).

- Readout-segmented EPI is another acquisition strategy, used in the majority my thesis work. In this variant of EPI, the EPI trajectory is split into segments to overcome phase error accumulation due to the long readout period. We will see in section 1.2.3 the motivations which led for this strategy more in detail.

![Diagram of EPI strategies](figure3.png)

**Figure 3:** Illustration of conventional, single-shot EPI and readout-segmented EPI strategies to encode the k-space. In the conventional k-space encoding, readout gradient is switching on to collect a series of points at regular k-intervals, one line every TR. Whereas, in single-shot EPI strategy, all k-space are acquired in one shot with a rapidly oscillating readout gradient causing the trajectory to alternate in the positive and negative directions in the readout axis. The k-space coverage for readout-segmented EPI is divided into segments of contiguous k-space sample in the readout direction.

### 1.1.5 DW sequence

Renal DWI is mostly based on a single-shot Spin Echo (SE) EPI. In a SE sequence, rephasing dispersion due to external field inhomogeneities is established with an additional rf pulse (180° in the transverse plane),
added after the traditional 90° rf pulse. In that way, signal loss due to inhomogeneities in the magnetic field is reduced and refocused spins produce a signal called the echo. The time between the 90° excitation rf pulse and the maximum amplitude in the signal echo is the echo time (TE).
The DW sequence includes an additional pair of diffusion gradient pulses on either side of the 180° refocusing pulse as originally proposed by Stejskal and Tanner [73] (Figure 4), in combination with a SE prepared sequence. The first diffusion gradient dephases the spins with a spatially varying additional magnetic field. The phase accumulated during the first diffusion gradient is:

\[ \phi(x) = \gamma G_x \delta x \]  

The dephasing term of molecular diffusion from a point \( x_1 \) to a point \( x_2 \) during the time between the two diffusion gradients is

\[ \Delta \phi(x) = \phi(x_1) - \phi(x_2) \]  

\[ = \gamma G_x \delta(x_1 - x_2) \]  

The second gradient, with opposite sign, exactly rephases the spins, in the case of no spin diffusion (\( \Delta \phi(x) = 0 \)). In the case of spin diffusion, rephasing is incomplete since the spins have moved and are not in the same position on the dephase and rephase gradients.

Diffusion-dependent signal attenuation can be measured by the average dephasing for a population of molecules with:

\[ e^{i(\Delta\phi)} = -\int_{-\infty}^{\infty} P(\Delta\phi) e^{i\Delta\phi} d(\Delta\phi) \]  

with \( P(\Delta\phi) \) the free diffusion probability density function. The statistical predictions about the macroscopic diffusion behavior of an ensemble of free water molecules can be approximated by a Gaussian distribution:

\[ P(\Delta\phi) = \frac{1}{\sqrt{2\pi(\Delta\phi^2)}} e^{-\Delta\phi^2/2(\Delta\phi^2)} \]  

\[ e^{i(\Delta\phi)} \] can therefore be written as:

\[ e^{i(\Delta\phi)} = -\int_{-\infty}^{\infty} \frac{1}{\sqrt{2\pi(\Delta\phi^2)}} e^{-\Delta\phi^2/2(\Delta\phi^2)} e^{i\Delta\phi} d(\Delta\phi) \]  

\[ = e^{-\Delta D} \]  

Typically, the high signal intensity on DW images comes from immobile spins. The relationship between the signal intensity (SI) in the presence of diffusion encoding gradients and \( S_{b=0} \) (the signal intensity without the application of diffusion encoding gradients) is:

\[ \frac{SI(b)}{S_{b=0}} = \frac{S_{b=0} e^{-\frac{TE}{T_2}} e^{-bD}}{S_{b=0} e^{-\frac{TE}{T_2}}} \]  

\[ = e^{-bD} \]  

The b-value parameter [units: s/mm²] depends on the specific gradient pulse sequence parameters. The degree of diffusion sensitization can be directly adjusted with the b-values, such that:

\[ b = \int_0^T dt [\gamma \int_0^t g(t') dt']^2 \]  

\( g(t') \) describes all the gradient characteristics that are applied during the time \( T \) between the rf excitation pulse and the formation of the echo. In the ideal case of rectangular shape gradient pulses, the b-value is given by:

\[ b = \gamma^2 G_d^2 \delta^2 (\Delta - \frac{\delta}{3}) \]
where $G_d$ is the amplitude of the diffusion gradient, $\delta$ the duration of each diffusion gradient, and $\Delta$ is the time interval between the onset of the two gradients before and after the refocusing pulse ($180^\circ$ pulse).

Diffusion gradients are applied in at least three orthogonal directions to obtain rotationally invariant measurements. In practice, gradient parameters $G_d$, $\delta$ or $\Delta$ are often not directly accessible to the user. The b-value calculation depends only on $G_d$.

Figure 4: Illustration of Stejskal Tanner spin echo pulse sequence (PGSE) for a diffusion-weighted acquisition. Two diffusion-sensitizing lobes with equal area and polarity ($G_d$) are added on either side of the $180^\circ$ refocusing pulse of a SE sequence. Molecules diffusing to new position between the first dephasing gradient and the second rephasing gradient pulse will not be rephased by the second gradients. Between the individual echoes, the phase-encoding gradient is switched on, in order to reach the next line in the k space. The number of echoes is the Echo Train Length (ETL) and the space between echoes is the Echo Spacing (ES).

1.1.6 Quantification of DWI and DTI

This subsection describes the most widely used fitting models for quantification of renal DWI (monoexponential, biexponential, stretched-exponential and kurtosis), as well as DTI.
ADC from monoeXponential fitting:

The monoeXponential model describes well the non-restricted diffusion in homogenous media. Following the equation (27), the slope of the logarithm of the normalized signal intensity gives the diffusivity parameter. Unlike in pure water, all different components and compartments (intravascular, extra and intra cellular) can change water molecules mobility. In vivo diffusivity differs from the true diffusivity and we refer to an Apparent Diffusion Coefficient (ADC) [mm$^2$/s]. The ADC parameter is the most common and simple way to quantify DWI. This parameter integrates the effects of all Intravoxel Incoherent Motion (IVIM), with the effects of both diffusion and perfusion. Assuming monoeXponential decay, the ADC is calculated for each voxel as:

\[
SI(b) = S_{b=0}e^{-b \times ADC}
\]

(29)

\(SI(b)\) is the signal intensity measured with the b-value \(b\). \(S_{b=0}\) is the signal amplitude in the absence of diffusion weighting.

A minimum of two b-values are needed in the monoeXponential model to generate a quantitative ADC map. ADC estimation is highly sensitive to the b-value sampling. A computation from at least three different b-values is often recommended. However, as the acquisition time depends on the number of sampling points, increasing the number of b-values will increase the total acquisition time. Many articles reported the use of 3 b-values such as \(b=0, 400, 800 \text{s/mm}^2\) or \(b=0, 500, 1000 \text{s/mm}^2\). In those particular cases, there is no added value to use 3 b-values instead of 2 b-values, as the ADC map is the same as images created using respectively \(b=0, 800 \text{s/mm}^2\) or \(b=0,1000 \text{s/mm}^2\) [59]. When using three symmetrical b-values, the slope (ADC) remains unchanged, only the y-intercept is affected.

Dt, D*, f from biexponential fitting:

The biexponential model for IVIM quantification was introduced by Denis Le Bihan and al. [48]. In this model, the two main contributions of the motion (molecular diffusion due to thermal Brownian motion and the microcirculation of blood, also called perfusion or "pseudo diffusion") is separated into two compartments such that:

\[
SI(b) = S_{b=0}((1-f)e^{(-D \cdot b)} + fe^{-(D^*+D) \cdot b})
\]

(30)

\(SI(b)\) is the signal intensity measured for a given b-value. \(S_{b=0}\) is the signal amplitude in the absence of diffusion weighting. \(D\) is the diffusion coefficient representing pure molecular diffusion (the slow component of diffusion), \(f\) is the perfusion fraction linked to microcirculation i.e. the fractional volume (\%) of capillary blood flowing in each pixel, and \(D^*\) is the "pseudo diffusion" coefficient i.e. the incoherent microcirculation within the voxel (perfusion-related diffusion, or fast component of diffusion). Perfusion within capillaries has no specific orientation and depends on the flowing blood and the vascular architecture. That is why it is referred as a type of pseudo diffusion. However, the rate of signal attenuation resulting from the pseudo diffusion is an order of magnitude greater than tissue diffusion because of the larger distances of proton displacement between the application of diffusion gradients.

Lemke et al. [50] investigated the vascular contribution to IVIM parameters, and proposed a modified version of the IVIM equation incorporating the difference in relaxation times of blood and tissues.
The Lemke correction with $T_1$ and $T_2$ is given by:

$$SI(b) = S_{b=0} \frac{((1 - f')e^{-\frac{bR_{tissue}}{T_1}}) + f'e^{-\frac{bR_{blood}}{T_2}}}{(1 - f')e^{-\frac{bR_{tissue}}{T_1}} + f'e^{-\frac{bR_{blood}}{T_2}}}$$

(31)

with $T_{1\text{tissue}}$, $T_{2\text{tissue}}$, $T_{1\text{blood}}$, and $T_{2\text{blood}}$ are the longitudinal and transversal relaxation times of tissue and blood, respectively. $D_{av}^*$ is the fixed average pseudo diffusion. $D'$ and $f'$ are the relaxation time compensated diffusion coefficient and perfusion fraction, respectively.

In our study, a significant reduction of the perfusion fraction $f$ was found for the cortex and medulla with the Lemke correction in Chronic Kidney Disease (CKD) patients, as shown in Figure 5. These differences were reduced and non significant for the cortico-medullary difference $\Delta f$. In this homogenous population of CKD patients, good correlations for cortex and medulla between corrected and non corrected $f$ (Figure 6) are measured with $R^2=0.97$ for cortex and $R^2=0.90$ for medulla. $D$ and $D^*$ did not change significantly with the modified version of IVIM.

Figure 5: Boxplot illustrating the Lemke correction in 10 CKD patients. A significant difference was measured between corrected and non corrected perfusion fraction $f$ for the cortex and medulla (Wilcoxon paired test). The difference was not significant when considering the $\Delta f$. 

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Figure 6: Correlations corrected and non corrected perfusion fraction of the cortex and medulla, as well as for $\Delta f$. Statistical dependence as a systematic bias between $f$ values were measured across corrected and non-corrected equation. In the pink box are all $r$ correlation coefficients.
Figure 7: DW images acquired at multiple b-values (10 b-values up to 900s/mm$^2$) and the corresponding decay of signal intensity fitted with a biexponential. First data points (b-value under 100s/mm$^2$), where there is a steeper slope, were associated with pseudo diffusion. By contrast, large b-values are less sensitive to contribution from microcapillary perfusion as the signal attenuation of the perfusing protons is essentially complete and therefore this region is associated with true diffusion.

To measure biexponential parameters ($D$, $D^*$ and $f$) at least four different b-values must be acquired. Significant difference in the biexponential parameters were found depending on the calculation methods used [34]. Three principal methods, using nonlinear least square fitting, have been described to calculate the biexponential parameters:

- Unconstrained free biexponential fitting [79, 86]:

  The optimum $\theta$ [$D$, $D^*$, $f$] is estimated by minimizing a sum of square cost function. Currently, the traditional Levenberg-Marquardt algorithm employed, is an iterative search based on a local approximation of the second derivative (Hessian) of $J(\theta)$, expressed as:

  $$J(\theta) = \sum_{i=1}^{N} \left( \frac{SI_i(b_i)}{S_{b=0}} - g(b_i, \theta) \right)^2$$  \hspace{1cm} (32)

  Algorithms for parameter estimation search the optimal $\theta = \text{argmin}_\theta J(\theta)$.

  Noise simulations have shown that the calculation of three free parameters can only be fitted reliably with sufficiently signal-to-noise ratio in DW images [86].

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• Segmented analysis as used in [69, 27]:

An initial estimation of $D$ is calculated using a reduced set of b-values with a monoexponential fitting. The b-value threshold is traditionally set at 250s/mm$^2$ to be sure to avoid perfusion effect. The low b-intercept of the monoexponential fit is used to calculate $f$ as:

$$f = \frac{S_{b=0} - S_{\text{intercept}}}{S_{b=0}}$$  \hspace{1cm} (33)

$D^*$ is then computed using the resulting $D$ and $f$ as fixed parameters.

• Fix $D^*$ to a predetermined value [49]:

$D^*$ is directly fixed with a given value according to prior studies (12.0µm$^2$/s [86, 34], 20.0µm$^2$/s ([65]) and used in the biexponential model to fit $f$ and $D$.

$\alpha$ and DDC from stretched-exponential fitting:

This model was introduced to characterize the deviation of the signal attenuation from monoexponential behavior and thus give an information on how intravoxel heterogeneity affects diffusion measurement [4]. The signal intensity is described as:

$$SI(b) = S_{b=0}e^{-b \times DDC \alpha}$$  \hspace{1cm} (34)

In comparison with the monoexponential equation, this equation yields two variables (DDC and $\alpha$). DDC represents the mean intravoxel diffusion rate. $\alpha$ the water molecule diffusion heterogeneity, which varies between 0 and 1. A $\alpha$ parameter close to 1 represents low intravoxel diffusion heterogeneity, approaching a monoexponential decay.

$D_{\text{app}}$ and $K_{\text{app}}$ from kurtosis fitting:

Diffusion kurtosis imaging (DKI) was established to provide characterization of non-Gaussian water molecule diffusion. DKI was first published by Jensen et al. in a study quantifying the degree to which water diffusion in cerebral tissues is non-Gaussian [41]. As the b-value increases (b≥1000s/mm$^2$), the logarithmic DW signal decay plot exhibits a parabola, leading to a positive deviation from the straight line plot of the Gaussian predictions. In DKI the signal intensity is described as:

$$SI(b) = S_{b=0}e^{-b \times D_{\text{app}} + \frac{1}{b} \times b^2 \times D_{\text{app}}^2 \times K_{\text{app}}}$$  \hspace{1cm} (35)

$D_{\text{app}}$ is the diffusion coefficient [mm$^2$/s], corrected to account for the non-Gaussian behaviour. Kurtosis is a term for describing the peakedness of a probability distribution. Kurtosis of ideal non-Gaussian diffusion gives the apparent diffusional kurtosis $K_{\text{app}}$ [unitless] =0, and:

$$ln\left[\frac{SI(b)}{S_{b=0}}\right] = -b \times D_{\text{app}}$$  \hspace{1cm} (36)

$D_{\text{app}}$ and $K_{\text{app}}$ give information on heterogeneity and irregularity of cellular microstructure. The feasibility of DKI for fibrosis and inflammation assessment was studied ex vivo in murine liver [2], with b-values up to 3500s/mm$^2$ (9.4T MR system). In that study, $D_{\text{app}}$ coefficients were found to decrease with increasing degrees of liver fibrosis (r=-0.74: 95% CI: -0.83 - 0.55) while $K_{\text{app}}$ increased with increasing fibrosis (r=0.74: 95% CI: 0.49 - 0.88). Only moderate Spearman rank correlations between DKI metrics and inflammation were measured. The strong positive correlation between $K_{\text{app}}$ and the increase of fibrosis could be due to hindered free diffusion.
**D_{mean}** and FA from Diffusion Tensor Imaging:

Diffusion tensor Imaging (DTI) is a development from DWI that accounts for the directionality of molecular diffusion and provides fractional anisotropy (FA). FA describes how much the diffusion deviates from isotropic (spherically symmetric) diffusion. In particular, the renal medulla diffusion is expected to be lower in the perpendicular direction than parallel to the preferred spatial orientation of the tubules [66, 43, 15, 12, 8, 84, 91]. This could be the reason for the lower renal medullary ADC compared to the cortical ADC. The diffusion tensor is given by:

\[
D = \begin{bmatrix}
D_{xx} & D_{xy} & D_{xz} \\
D_{yx} & D_{yy} & D_{yz} \\
D_{zx} & D_{zy} & D_{zz}
\end{bmatrix}
\]

To measure the diffusion tensor, at least 6 encoding directions are needed. A good compromise between acquisition time and resulting image quality was found for 15 directions [12]. The mean diffusivity D_{mean} (corresponding to ADC when only three directions are acquired) describes the diffusion coefficient average over all directions, and is expressed as:

\[
D_{mean} = \frac{D_{xx} + D_{yy} + D_{zz}}{3}
\]

(37)

To calculate FA, the matrix is first transformed into a diagonal matrix such that:

\[
D = \begin{bmatrix}
D_1 & 0 & 0 \\
0 & D_2 & 0 \\
0 & 0 & D_3
\end{bmatrix}
\]

D_1, D_2, D_3 are the eigenvalues of the eigenvectors ν1, ν2, ν3, respectively.

Finally, FA ranges from 0 (fully isotropic) to 1 (fully anisotropic) and is given by:

\[
FA = \sqrt{\frac{3}{2}} \sqrt{\frac{(D_1 - D_{mean})^2 + (D_2 - D_{mean})^2 + (D_3 - D_{mean})^2}{D_1^2 + D_2^2 + D_3^2}}
\]

(38)

**Discussion:** Monoexponential and biexponential models are the most commonly fitting methods used in renal DWI to describe IVIM. The monoexponential model has shown to be the most robust against noise [86]. However, the calculation of ADC by simple monoexponential fit of the MR signal with the b-values does not fully describe the complexity of the tissue. The biexponential model appears to be better adapted to the DW data. However, biexponential parameters are highly variable because of the use of one equation for 3 unknown parameters. At high b-values (> 1000s/mm^2), other fitting models, such as the stretched-exponential and the kurtosis models were developed to assess tissue heterogeneity. However, the maximum b-value currently achieved in renal DWI is 900s/mm^2. DTI with its multiple directions requires more advanced post processing techniques and an increase of the total acquisition time, but it could be an interesting tool to assess renal pathologies.
1.2 Clinical application of renal DWI

1.2.1 Context

Overview of the kidney parenchyma:

Kidneys are the organs responsible for removing excess water, salts, toxins and urea from the blood stream. The kidneys are paired, bean-shaped organs that lie on either side of the spinal column in the retroperitoneal space. Each kidney is embedded in a thick layer of perirenal adipose tissue (the renal capsule) containing the renal parenchyma. The Figure 8 shows the two layers of the renal parenchyma: the cortex and medulla. The renal cortex contains the major part of the nephron, which is the functional unit of the kidney. The cortex is composed of the renal corpuscle formed by the glomerulus (network of capillaries) and the Browman’s capsule, which is cup-shaped, where filtration occurs. The renal medulla has a pyramidal structure where the collecting ducts are located. These pyramids are striated due to the presence of these ducts. The renal medulla contains the loops of Henle and the collecting tubules where water reabsorption occurs.

![Figure 8: Left healthy kidney in coronal cross-section on T2-weighted half-Fourier acquisition single-shot turbo spin-echo. The cortex is the outer, continuous layer of the kidney. The medulla is the inner region, in pyramidal form (in pink), of the kidney.](image)

Chronic Kidney Disease:

Chronic Kidney Disease (CKD) is usually defined as more than 3 months of altered structure and/or function of the kidney. Prevalence of CKD is estimated to be, for example, from 6.3% (95% CI 6.0-6.5) in Norway, 10% in Switzerland with 5% of Stage III and higher (equivalent to a loss of 40% or more of kidney function) to 25.6% (95% CI 23.7-27.5) in Germany [31, 7]. Apparition and progression of interstitial fibrosis in the kidney tubulo-interstitial space, with progressive loss of normal structure, is the most predictive element of CKD. Interstitial fibrosis is the common injury pathway contributing to kidney structural deterioration and loss of function [68, 22]. CKD is characterized by an increase of synthesis and deposition of extracellular matrix.
components within the tubulointerstitial space (interstitial fibrosis) and glomeruli (glomerulosclerosis). Kidney interstitial fibrosis occurs primarily in the renal cortex before affecting the renal medulla. Several articles have reviewed the key features of the fibrosing kidney, including an extensive review of recent advances and remaining barriers to image kidney fibrosis by Leung et al [52]. The hypothesis is that the restriction in water mobility is mainly due to collagen infiltrate of the extracellular space in high-grade fibrosis as illustrated in Figure 9. An increase of interstitial fibrosis should lead to a restriction of water molecule diffusion in the cortical tissue. For this reason, DW parameters yield interesting biomarkers to assess kidney fibrosis.

Figure 9: A normal case of diffusion process in a healthy tissue ie cortex without fibrosis from histology (A), and the case of a patient with high-grade of interstitial fibrosis (B). The collagen fibers were stained with Masson trichrome protocol. The clinical pathologist estimated the percentage of fibrosis to 80%. The proportion of collagen fibers is believed to reduce Brownian water motion within fibrotic tissues.

Kidney biopsy, the gold standard for fibrosis assessment:

Currently, the gold standard to monitor in situ kidney interstitial fibrosis and inflammation is histology obtained from needle biopsies. Biopsy is an invasive procedure, impeded with several inherent limitations. First, biopsy is associated with risk of hemorrhage complications in a number of cases, limiting its repeated use. Second, sampling errors due to the small samples size (about 2mm in diameter) can lead to inadequate
or non-representative histology material for the analysis. The sample kidney tissue may not reflect the true degree of interstitial fibrosis, leading to a direct error in the diagnostic work-up. In addition, biopsy almost never includes the medulla. The lack of non-invasive tools to reliably assess interstitial fibrosis motivates clinicians and researchers to look for more robust and safer non-invasive biomarkers, assessing the whole organ as well as regional variations. In that context, DWI is particularly interesting for kidney assessment. DWI does not require Gadolinium contrast agent exposure, which is associated with Nephrogenic Systemic Fibrosis (NFS) in patient with renal failure. Most commonly reported in end stage renal disease, NFS is associated with progressive and severe fibrosis of the skin and other organs that can lead to mortality.

1.2.2 State-of-the-art

ADC from monoexponential fitting:

ADC decreases in renal lesions and masses [14, 72, 76, 87, 85], renal artery stenosis [86], acute kidney injury [37], ureteral stone obstruction [79, 80], pyelonephritis [23, 82, 64], transplant function and acute transplant rejection [79, 20]. In renal interstitial fibrosis assessment, Inoue et al. first reported a negative correlation between water diffusion as measured by DWI and interstitial fibrosis as measured by histology on kidney biopsy in 76 non-diabetic CKD patients [39]. In 2014, two independent studies measured a decrease in ADC with the increase of fibrosis degree in CKD patients [54, 90]. Li et al. found a significant, but rather weak, correlation ($R^2 = 0.40$) between ADC and a global pathological score derived from the biopsy [54]. Zhao et al. confirmed the negative correlation between ADC and histological fibrosis score obtained in 25 CKD patients [90]. In this study, the correlation between these two parameters was improved ($R^2 = 0.61$) probably reflecting the higher magnetic field (3T c.f. 1.5T) and consequent higher SNR. The correlation between ADC and renal fibrosis indicates the potential of DWI to reduce the number of biopsies needed in some groups of CKD patients.

On the other hand, ADCs of the abdomen suffer from medium to high contamination from perfusion effects, which poses the question of its limits. Zhang et al. simulated the variability of ADC associated with the use of the monoexponential model and different b-value sets [88]. The limitations of the monoexponential model in renal studies have been raised, especially due to the high variability in the reported ADC values in the literature. It was suggested either that data for monoexponential analysis should be acquired at a fixed set of b-values or, that a biexponential model should be used. Monoexponential fitting error of diffusion decay data from the cortex, medulla, whole kidney and renal cyst were significantly higher than with the biexponential model. The monoexponential model is then an approximation for tissue diffusivity. By including the low b-values (under 200s/mm$^2$), the ADC contains both perfusion and diffusion. This is particularly true when the perfusion fraction is more than 20% as is the case in the kidney. Though it is useful to quantify both these effects, it is not possible by a simple monoexponential fitting to separate the two influences. In patients, Thoeny et al. highlighted that renal artery stenosis and ureteral obstruction are accompanied by renal perfusion changes [77, 79], which would be missed if the monoexponential model were performed with a non-adapted choice of b-values.

$D_t, D^*, f$ from biexponential fitting:

A biexponential function fits the signal decay better than the monoexponential model. The biexponential model is recommended under the precondition of sufficient signal to noise ratio [86]. On one hand, some authors found biexponential parameters more suitable than ADC and encourage using this model in renal applications. In particular, the diagnostic performance of biexponential parameters was better than ADC for renal tumor assessment [10, 9, 17]. Chandarana et al [9] found higher accuracy with the perfusion fraction $f$ (measured with an area under the receiver operating characteristic curve of 0.74), compared to ADC (0.67) for the diagnosis of renal tumor. Ichikawa et al. [38] worked on the alterations in diffusion and perfusion in 365 patients with renal dysfunction. Patients were divided in groups according to their renal function, estimated with the estimated glomerular filtration eGFR level [mL/min/1.73m$^2$]. ADC was the least relevant factor compared to $D^*$ to separate groups of different eGFR. Renal cortex $D^*$
could differentiate groups with eGFR higher than 80 mL/min/1.73m² from those with eGFR level under 80 mL/min/1.73m². Whereas ADC was only lower in patients with eGFR level less than 60 mL/min/1.73m². As renal dysfunction progresses, renal cortical perfusion might be reduced earlier and affected more than diffusion. On the other hand, biexponential parameters are considered as highly variable compared to ADC [71, 71, 3]. Some concerns have been raised regarding the utility of the biexponential model to measure true vascular perfusion in kidney, and for a clear discrimination of tissues [17, 60, 57, 20]. Pekar et al [60] showed that D* is highly variable (above 20%) unless an unrealistically high SNR is achieved. The range of f values is also wider in the literature within 20-50%, at a standard deviation beyond 25% [78, 79, 21, 86, 5, 65].

Non-gaussian fitting models (stretched-exponential and kurtosis):

The diffusion heterogeneity α index was useful for differentiating renal clear cell carcinoma and minimal fat angiomylipoma [53]. However, ADC also allowed the differentiation of both pathologies [53, 74, 75]. Also, DKI [61, 35, 16, 44] was not yet investigated for clinical renal DWI. A major limitation came from the fact that renal DWI is typically performed using a maximum b-value up to 800-900 s/mm² to have a sufficient SNR. Subsequent quantification is performed assuming Gaussian diffusion behaviour. In addition, the kurtosis model is particularly challenging as sources of non-Gaussian behaviour can be added and mis-interpreted, such as the Rician distribution that gives signal intensity bias or also, partial volume effect [45]. In conclusion, a non-gaussian model for DWI data fitting, such as stretched-exponential model and DKI is of little interest to assess kidney disease.

D_{mean} and FA from Diffusion Tensor Imaging:

The added value of DTI compared to ADC from DWI with 3 encoding directions is still under debate. Previous studies showed a strong relationship between FA and renal allograft function, evaluated either by creatinine clearance [58] or eGFR [36, 46, 24]. A lower FA was associated with the magnitude of GFR reduction. However, in these studies, a decrease of ADC was also reported, and a direct comparison was not performed to evaluate the real added value of the FA parameter in comparison to ADC. In another renal DTI study measuring the degree of fibrosis on renal biopsy in CKD patients with glomerulonephritis, there was less clear separation between CKD stages 1-3 with FA as compared to ADC [25]. Examples of FA maps are given in Figure 10.
Figure 10: (A) FA maps of one healthy volunteer, acquired with 6, 20 and 64 directions. (B) FA maps of three allograft patients with different level of interstitial fibrosis (images acquired with 64 directions).

Figure 10 shows the effect of increasing diffusion gradient direction number on DTI in a healthy volunteer (A). The qualitative evaluation showed that DTI with 64 directions gave a better cortico-medullary difference than DTI acquired with 6 and 20 directions. This is illustrated in three allograft patients (B).

1.2.3 Major limitations in renal DWI

Despite promising results, there is a need to counteract several technical limitations to make renal DWI a sequence of choice in CKD patient care. The main limitation is the huge variability in ADC values found in the literature [88], even within a single study. It is therefore difficult to compare directly ADC values and provide a threshold for diagnosis. Artifacts that degrade DW image quality are the most noticeable sources of variability. Kidneys are affected by specific artifacts caused by intestinal peristalsis and respiratory motion due to their localization in the abdomen. In addition renal status differences induced by flow, cardiac-driven pulsation and hydration level can lead to variability in diffusion parameters. Possible sources of variability (technical and human) are summarized in Figure 11. In the following text, we address three important sources of variability in kidney DWI: the acquisition variability related to the choice of the b-values and the EPI strategy, and the motion artifacts particularly problematic in kidney DWI.
Figure 11: Each one of the steps presented are potential sources of variability that can lead to substantial errors. Variability may come from the acquisition (difference in gradient performances and sequence setting), post-processing (non-adapted monoexponential fitting, segmentation with variability in regions-of-interests placement) or due to physiological variations (sampling bias in biopsy, motion, difference in hydration level).

Choice of the optimum b-values:

The number and distribution of b-values vary greatly among researchers, resulting in a variation in the IVIM parameters. The choice of optimum b-values is still under debate. Two recent papers [51, 89] investigated the question of the optimum b-values for abdominal DWI by simulations and in vivo validation in volunteers. Lemke et al. was the first to use the error of the fit obtained with the Monte-Carlo simulations as optimization criterion to find the optimal distribution [51]. The optimum b-value distribution for a medium perfusion range (as in kidney) was found to be a complex interleaved series of 36 b-values, specifically 0, 40, 1000, 160, 150, 40, 680, 150, 200, 940, 170, 990, 440, 740, 40, 230, 360, 0, 270, 70, 270, 870, 0, 40, 940, 60, 320, 240, 0, 260, 60, 1000, 920, 310, 1000, 50 s/mm². Zhang et al. found that with an optimal set of b-values, consisting of multiple repetitions of four distinct b-values, it is possible to improve the precision of biexponential parameters by 20-30% [89].

EPI artifacts in kidney DWI:

Previous reviews already reported some of the artifacts encountered in the case of head single-shot EPI DW imaging [42]. The two majors challenges reported were eddy currents [40], and susceptibility artifacts. These artifacts are also present in kidney DWI (Figure 12). Eddy currents come from gradient switching and can lead to temporal shift in k-space. The data acquired along one readout direction may not align exactly with those in the opposite direction resulting in Nyquist ghosting and distortions. Ghosting on DW images is discernable by a replication of the tissue along the phase encoding direction. The use of bipolar gradient pulses [1] to balance eddy-current is implemented in clinical MR systems. Currently, eddy-currents are sufficiently corrected, and the amplitude of the effect is too weak to visibly deteriorate DW images quality.
Major challenges in the application of DWI to kidney imaging come from the long readout of the EPI acquisition strategy. Single-shot EPI is more prone to artifact than conventional imaging. The long readout period leads to a narrow bandwidth per pixel in the phase encoding direction compared to the pixel bandwidth in the readout direction, by a factor equivalent to the number of k space lines. The associated effects are large fat-water shift and off-resonance effects. Chemical-shift effects lead to constructive and destructive interference between signals at different frequencies. The result is a spatial shifting of the fat signal in the image. Off-resonance effects lead to geometric distortion in the presence of $B_0$ inhomogeneities and susceptibility variations. Susceptibility variations translate to variations of the Larmor frequency of spins and thus to phase errors in the k-space that accumulate over the duration of the echo train. The position of the kidney, directly neighboring the intestines which are filled with air, means that the air/tissue interface can cause serious distortion related to an inhomogeneous magnetic field. This property of the EPI sequence is a severe limitation for its application in kidney. To counteract the strong local variations in magnetic field strength, at the interface of tissue-air, an option is to locally re-homogenize the local magnetic field by shimming. However, this is insufficient in kidney DWI to fully remove all artifacts. Another directly related disadvantage, is the relatively low apparent spatial resolution associated with kidney DWI due to the rapid
\( T_2 \) decay of the signal during the gradient echo train, which results in a blurring. Also, \( T_2 \) relaxation time determines the signal intensity of tissues on DW images. The relatively short \( T_2 \) value of kidney (compared to the brain) leads to a rapidly decreasing signal from kidney tissues, and thus the kidney requires much shorter TE than brain tissues. In the following text some solutions are proposed to shorten the readout and reduce artifacts linked to single-shot EPI.

- **Parallel imaging:** A major innovation, that made EPI acquisition accessible outside the brain, was the implementation on clinical MR scanners of accelerating methods, such as parallel imaging. Abdominal imaging requires a large field-of-view (FOV), at least the size of the abdomen, to satisfy the Nyquist criterion. The spacing between k-space points in each direction is inversely proportional to the FOV in that direction. The highest frequency collected in k-space (\( k_{\text{readout, max}} \) and \( k_{\text{phase, max}} \)) is inversely proportional to the image resolution. Thus, the FOV and the matrix size can be manipulated by changing the number of points and the space between these points of the k-space. In parallel imaging, the amount of k-space data collected is undersampled in the phase-encoding direction. With this method, a fraction \( 1/R \) of the total k-space lines is acquired in order to reduce the acquisition time by a factor R. Phased-array coils, such as the body 18 channels coil used for abdominal imaging, contain several coil elements that together provide a signal extended to a larger FOV. Each coil element has a localized sensitivity profile. Individual images from each component coil can be combined using knowledge of the position of the coil in the FOV and a sum of squares reconstruction method [67], or other array reconstruction methods [83]. The two commonly used parallel imaging techniques are GeneRalized Autocalibrating Partially Parallel Acquisitions (GRAPPA)-type reconstruction from the under-sampled data (k-space) [30] and SENSitivity Encoding (SENSE) -type reconstruction from aliased images (image domain) [63].

Acceleration methods help to reduce long readout based distortion artifacts. However, there is still room for improvement for kidney DWI.

- **Readout-segmented EPI:** Another approach to reduce EPI artifacts is to divide the readout trajectory into multiple segments to shorten the duration of readout. By shortening the echo train length, the readout-segmented EPI is less sensitive to susceptibility variations (distortions and blurring effect). The net penalty of this strategy is that the total acquisition time must be increased by a factor equal to the number of segments, since the excitation pulses for each segment is separated by a repetition time. Porter et al. developed and implemented 2D DWI with a Readout Segmentation Of Long Variable Echo Train (RESOLVE) [62] for Siemens including a two-dimensional navigator-based reacquisition. This navigator provided a correction for the nonlinear phase errors that arise from head motion. However, 2D navigator phase correction fails when the spatial frequency of the motion-induced errors becomes too large, as is typically the case in kidney imaging. Figure 13 shows \( b_0 \) images of a fluid-filled phantom acquired with single-shot EPI and RESOLVE.
Figure 13: Comparison between single-shot EPI and readout-segmented EPI (5 shots) in a fluid-filled phantom (Picker International, model No 374486). The corresponding half-Fourier acquisition single-shot turbo spin-echo (HASTE) image is shown in the first image and served as reference for the anatomical structure. Strong distortions are clearly more visible on single-shot EPI compared to readout-segmented EPI.

Motion artifact in kidney DWI:

Motion corrupts data in renal DWI. These motion artifacts can be due to patient voluntary (sudden position changes) or involuntary movements (such as physiologic motion). Motion can be classified in two categories: periodic motion (respiratory motion, cardiac motion, blood pulsation) and non-period (gastrointestinal peristalsis). In addition, the different type of motion can be separate into the following categories: rigid body or bulk motion (translations and rotations), elastic motion (stretching, compression) and flow (laminar blood flow in vessels). All motion categories induce incorrect position of data points in k-space, which in turn induce degradation of DW quality in the image domain. However, motion-related artifacts depend on the category of the motion. Motion between k-space data acquisitions, which leads to a shift of the kidney in the image domain, can be manually or automatically registered [70]. Motion during imaging, when gradients are switched on in the pulse sequence, lead to data inconsistencies between k-space lines, resulting in ghosting and/or blurring in DW images. Streaking artifacts occur in case of rotation during the k-space data acquisition. When the motion takes place between the periods of application of DWI encoding gradients, spins acquire additional phase that is a confounding factor in the analysis producing artificial signal voids.

Motion was problematic from the beginning of the project with the apparition of stripes within DW images (Figure 14). The spin history excitation effect, called spin-history artifact [18, 29], appears with out-of-plane motion between slice-selective rf pulses and causes alteration in image contrast. This artifact is not documented in renal DWI and originates from multi-packet interleaved slices. Stripe artifact slice-to-slice signal intensity variation is present for the same b-value in the fit, but not visible on a phantom. This artifact is due to the combined effect of interleaving acquisition and motion in single plane. Spin-history artifact occurs when TR ≪ 5T1 of tissue. Not all spins in the packet hade the same relaxation rate, leading to differences in signal intensity.

Numerous methods to mitigate or correct for motion artifact-induced degradation of DW images have been developed. However, not all methods are commercially available and no single method can correct for all types of kidney-related motion. The simplest method to avoid respiratory artefacts is to perform DW acquisition in breathhold. However breath holding restricts scan duration and requires patient compliance. The limited acquisition time means breath holding suffers from low signal-to-noise ratio, which in turn limits the image quality [55]. Synchronizing the acquisition with the underlying periodic motion can allow free-
breathing DW sequence. Currently, all clinical MR systems offer triggering, gating or navigator methods depending on the constructor and the DW sequence. However, this is often insufficient to correct for all kidney motion, which therefore constitutes a challenge in kidney DWI.

![Figure 14](image.png)

Figure 14: Top images are multi-planar reconstructed of a right kidney DW images. A, B and C represent coronal acquired, axial reconstructed and sagittal reconstructed orientations, respectively. Three slices have hyperintense signal compared to other slices. In the bottom row is the same volunteer acquired without the artifact (D, E, F). The artifact was removed by avoiding interleaved slice acquisition and concatenations. Here slices are acquired in sequential slice order.

### 1.2.4 Aim of the thesis

The renal diffusion study is part of the current effort made by a research and clinical collaboration for the radiology and nephrology departments of the Geneva University Hospitals. The overall aim is to develop a tool or set of tools to better assess chronicity and activity of chronic kidney disease. This project has involved myself, a physics PhD student, to develop a MRI approaches for clinical assessment of CKD. Specifically, my work addressed the challenges of susceptibility and motion artifacts that impact image quality and diagnosis in renal DWI, and therefore prevents mainstream clinical use. Resolution of theses problems would enable a robust non-invasive technique of obvious benefit to the patient over the current standard of care of repeated biopsies. An important effort was devoted to validating an MRI acquisition protocol in small animal models and healthy volunteers before it was applied in a large cohort of patients. Major results, leading to 3 publications [28, 26, 27] and two publications in preparation, were achieved and are presented in this manuscript.
2 Publications
2.1 Publication 1

Optimization of the acquisition strategy with RESOLVE as a new renal DWI

The goal of this first publication was to investigate the advantages of the RESOLVE strategy for distortion and blurring artifact reduction, and to develop tools to quantify the improvements in image quality.

An important part of this thesis was devoted to the development of small animals studies on a clinical MR scanner. The main motivation of using a clinical MR scanner for rodent imaging was the translational research approach. In that way, tools developed on rodent can directly be applied in patients since the same MR system is used. Also, results obtained from animal studies are more likely to be reproducible in patients since they have been acquired using the same hardware. However, rodent imaging is particularly challenging, especially on a clinical MR system with limited SNR and resolution.

The first aim of this PhD work concerned the optimization of the acquisition protocol, in order to make rodent DWI possible on a clinical 3T MR system. The DWI sequence used for small animal imaging was based on the single-shot EPI used for human kidney imaging. We adapted the parameters to allow rat imaging. However, the literature-based protocol had sub-optimal resolution and strong susceptibility artifact (image distortion and blurring) related to EPI acquisition. Improvements in the method were needed because DWI was not robust regarding image quality. Some DW images were unusable, with the kidney completely distorted. The basic idea was to use a segmented acquisition to reduce susceptibility artifact observed with ss-EPI (introduction section 1.2.3).

The following publication was the product of a fruitful collaboration with David Porter from Siemens, who developed the Readout Segmentation of Long Variable Echo Train (RESOLVE) sequence, proposed as a work in progress (WIP), for head DW imaging. Even though the initial goal was small animal imaging, we quantified the improvement of the RESOLVE sequence in a phantom and in healthy volunteers before considering this DW strategy in two small animal models of interstitial fibrosis. It was important to verify beforehand that RESOLVE brought an improvement in the DW image quality, compared to the classical single-shot EPI sequence, before starting small animal studies. The usefulness of this acquisition strategy was shown in volunteers in the first publication presented hereafter. Part of the study associated with the assessment of interstitial fibrosis in small animal models was presented in the second publication of this PhD work [26].

An important challenge of this study was to adapt RESOLVE an MR sequence developed for brain imaging to a moving organ, such as the kidney. The 2D navigator based reacquisition scheme, implemented in the sequence for correction of small head movements, was not sufficient to correct for kidney motion. We therefore implemented a homemade respiratory-gating system. In humans, a respiratory-gated implementation combined a small animal system with a human belt (Figure 15). This was proposed in order to overcome the initial limitation of gating strategy in the WIP. Significant image quality improvements were achieved compared to single-shot SE-EPI protocols. A significant reduction of geometric distortions and T2* blurring effects, were measured in a phantom, healthy volunteers and CKD patients, using in-house post processing tools. With RESOLVE for renal DWI, it became possible to reliably differentiate the diffusion difference between the cortex and the medulla. All these achievements opened perspectives for the localization and quantification of renal fibrosis, and justify its use in patients.
Figure 15: Scheme of the experimental setup for a respiratory-gated implementation of RESOLVE with monitoring small animal system SA Instruments, Inc, StonyBrook, NY11790 USA.
Original contributions

Improve the renal diffusion-weighted magnetic resonance imaging with readout-segmented echo-planar imaging at 3 T

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Abstract

Purpose: To assess the feasibility of a respiratory-gated implementation of readout-segmented SE-EPI (RESOLVE) for renal diffusion-weighted imaging (DWI) by comparison with single-shot SE-EPI (ss-EPI) in a phantom, healthy volunteers and chronic kidney disease (CKD) patients.

Materials and Methods: A fluid-filled phantom, 20 healthy volunteers and 10 CKD patients were scanned with the same parameters and coils on a 3 T MR system with 3 DW sequences (b-values = 0, 300, 500, 900 s/mm²): a standard ss-EPI (Reference EPI), a ss-EPI with higher resolution, bandwidth and acceleration factor (HR-EPI) and RESOLVE with the same spatial resolution as HR-EPI but a segmentation of the readout into 5 shots. Geometric distortions, image blurring using a ‘Canny’ edge detection based measure, cortico-medullary differentiation measured on b₀ images and ADC quantification were compared between the 3 sequences using one-way analysis of variance (ANOVA) with post-hoc Bonferroni (p < 0.05 was taken as statistically significant).

Results: RESOLVE reduced significantly geometric distortions and blurring and improved, in the volunteers and patients, the sharpness score by 56% on average in comparison to ss-EPI (p = 0.02). In healthy volunteers, the cortico-medullary differentiation with RESOLVE was also possible on a wider range of b-values (p < 0.02) with ADC values (in 10⁻⁶ mm²/s) of 1994 ± 246 in the cortex and 1762 ± 238 in the medulla (p = 0.001). In CKD patients, ADC values (in 10⁻⁶ mm²/s) from the RESOLVE sequence were not different between the cortex (1755 ± 145) and the medulla (1799 ± 163, p = 0.49).

Conclusion: Despite a longer scan time, RESOLVE enhanced significantly the quality of renal diffusion-weighted images by improving the difference in SI and ADC between the renal cortex and medulla in healthy volunteers. In CKD patients, RESOLVE showed a disappearance of this cortico-medullary ADC difference. These improvements justify further clinical studies.

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1. Introduction

Diffusion-Weighted MR Imaging (DWI) has shown promising results to differentiate pathological from healthy tissues in renal tumors [1], transplant rejection [2], pyelonephritis [3], ureteral stone obstruction [4] and renal artery stenosis [5]. DWI techniques used in the abdomen rely on single-shot diffusion-weighted echo-planar imaging (ss-EPI) which is sensitive to image artifacts [6]. The trade-off between resolution and signal-to-noise ratio for the large FOV used in the abdomen imposes an increased matrix size and therefore a longer EPI readout time. The sequence becomes more sensitive to in-plane geometric distortions caused by the off-resonance water protons in areas where a significant difference in susceptibility exists. In renal DW applications, severe distortions are present at the bowel (filled with air) and tissue interface.

One solution to improve the distortions in diffusion MRI is to use a ‘Readout Segmentation Of Long Variable Echo-trains’ (RESOLVE) MR sequence in combination with parallel imaging technique, such as GRAPPA, GeneRalized Autocalibrating Partially Parallel Acquisitions. The RESOLVE strategy is based on a segmentation of k-space into several shots along the readout direction in order to shorten the echo spacing. RESOLVE combined with parallel imaging was previously introduced by Porter et al. for acquiring high-resolution DW images with low susceptibility based image distortion and T₂ blurring in the brain [7]. This strategy has been validated in non-triggered applications, such as in head and breast imaging to...
reduce sensitivity to susceptibility artifacts [8–10]. RESOLVE outperformed ss-EPI for analysis of the pediatric brain in regions prone to geometric distortions, such as the orbit, the skull base, and the posterior fossa [11]. By comparison with a conventional ss-EPI sequence, RESOLVE has improved the lesion-to-background contrast and the categorization between benign and malignant breast lesions [12]. For these reasons, we hypothesized that RESOLVE could improve the robustness against artifacts that are a consequence of the long k-space sampling in renal DWI. We proposed in this study an implementation of a respiratory-gated RESOLVE protocol for kidney DWI as well as a comparison of image quality with a different implementation of ss-EPI in a phantom, healthy volunteers and chronic kidney disease (CKD) patients.

2. Materials and methods

2.1. Subjects

Twenty healthy volunteers, comprising 11 females and 9 males, with a mean age of 28.8 ± 4.7 years (range, 23–39 years) and ten patients, comprising 4 females and 6 males, with a mean age of 55 ± 16 (ranges 26–78 years), were recruited after informed consent. Healthy volunteers enrolled in this study had no known kidney disease. All patients were chronic kidney disease (CKD) patients, comprising 1 native kidney and 9 allograft patients. The patients’ characteristics are summarized in Table 1. The study protocol was approved by the local ethics committee (reference no. CER-1-160).

2.2. Phantom study

A standard cylindrical phantom filled with deionized water doped with phenol, sodium chloride and copper sulphate (Picker International, model No 374486, diameter 18.7 cm) was used in the experimental comparison.

2.3. MRI technique

The phantom, healthy volunteers and patients were scanned with the same imaging parameters and coils on a MAGNETOM Trio ‘Tim system’ clinical 3 T MR (Siemens AG, Erlangen, Germany) with a 200 T/m/s slew rate capability. In all cases, the images were acquired using the 6 element phased–array abdominal coil and the spine coil integrated into the scanner table. The protocol included two navigator-triggered ss-EPI MR scans using PACE (prospective acquisition correction technique) and the RESOLVE diffusion-weighted SE-EPI (Spin Echo based EPI) acquisition synchronized to the patient respiration using a respiratory belt. The use of a navigator to trigger ss-EPI DWI was chosen as it improves image quality and enables a more precise ADC quantification in the liver, compared to free breathing [13]. The first navigator-triggered ss-EPI was implemented with the parameters recommended for clinical practice [14,15] hereafter called ‘reference EPI’, and the second MR sequence was optimized for a higher resolution with an increased matrix, bandwidth and acceleration factor, called hereafter ‘HR-EPI’. In all the 3 diffusion MR sequences (ss-EPI and RESOLVE), a bipolar diffusion scheme was used instead of a monopolar approach to decrease eddy current effects resulting from the diffusion-encoding gradient pulses [16]. The diffusion-encoding gradients were applied in 3 orthogonal directions with 4 b-values (0, 300, 500 and 900 seconds/mm²). All DWI sequences were performed using the parallel imaging GRAPPA technique (acceleration factor = 2 for reference EPI and 3 for HR-EPI and RESOLVE) with the acquisition of 6 coronal–oblique slices of 5 mm each covering the kidney. Shim settings and image positioning were strictly identical for all DW imaging sequences. The different DW sequence parameters used for the study for both phantom and in vivo (healthy subjects and patients) scans are summarized in Table 2. A gradient echo (GRE) sequence with parameters TR/TE = 711/1.09 ms, flip angle 35°, FOV 379 × 328 mm, matrix size 192 × 133 mm, slice thickness 5 mm, acceleration factor 2, bandwidth 930 Hz/pixel was also performed to give reference anatomic images for the comparison of edge geometric distortions and region of interest (ROI) positioning in volunteers and patients.

2.4. Analysis of phantom studies

2.4.1. Geometric distortions

The level of geometric distortions was quantified with the use of the phantom to benefit from stable and reproducible conditions without the disadvantages of physiological noise or motion that could occur during the MR acquisition in a volunteer. For quantitative evaluation of geometric distortions, the DW images were resampled to have an identical matrix to the GRE images. Then, the diffusion images and GRE images used as reference were fused with the OsiriX fusion tool plugin (OsiriX Open source http://www.osiriX-viewer.com/). Geometric distortions were measured as the maximum distance in the phase-encoding direction between the phantom edges of the diffusion image and of the GRE image on the fused image.

2.5. Analysis of in vivo images

2.5.1. Geometric distortions

Geometric distortions due to susceptibility artifacts were qualitatively evaluated on the b₀ images. The contours of the kidney were drawn manually on the GRE images of healthy volunteers and patients and copied to all DW images with the OsiriX ROI tool.

2.5.2. Blurring

The T₂⁎ blurring effect due to the peak broadening of the point-spread function (PSF) [17] was evaluated on the RESOLVE and HR-EPI images only, as they had comparable resolution. Reference EPI was not included in this evaluation, as the lower resolution would not give comparable results. To compare the image degradation, an algorithm based on a ‘Canny’ edge detector [18] was developed with MATLAB® (R2012b, MathWorks, USA) to detect the renal edges and quantitatively evaluate the sharpness of the kidney.

Table 2

<table>
<thead>
<tr>
<th>DWI MR parameters.</th>
<th>Reference EPI</th>
<th>HR-EPI</th>
<th>RESOLVE</th>
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</tr>
<tr>
<td>b-values [s/mm²]</td>
<td>0, 300, 500, 900</td>
<td>0, 300, 500, 900</td>
<td>0, 300, 500, 900</td>
</tr>
<tr>
<td>Mean scan time</td>
<td>1'7&quot;</td>
<td>1'11&quot;</td>
<td>5'63&quot;</td>
</tr>
</tbody>
</table>
After image normalization, the same ROI was manually defined around the kidney on the images of both sequences. The selected region encompassed the entire kidney as closely as possible to avoid confounding pixels from other organs. The image was smoothed by a Gaussian filter ($\mu = 0.1, \sigma = 1$) to reduce the noise, and then the gradient of the image was computed. After getting gradient images, non-maximum suppression was done to find edges in the gray-scale image by looking for local maxima in the direction of gradient with pixels checked for a local maximum in their neighborhood. After the full scan of the image to remove any unwanted pixels that were not classified as a real edge, a hysteresis thresholding discarded non-edge pixels based on their connectivity. Two thresholds were used to perform the hysteresis thresholding in order to track the remaining pixels that had not already been suppressed. The sensitivity threshold was set empirically to 0.4 for the upper threshold (UT) and to 0.16 for the lower threshold (LT) (automatically calculated as 40% of the UT). If the gradient intensity of the pixel was higher than UT, the pixel was accepted as forming an edge and was set to a white pixel in a binary image. Otherwise, if the gradient intensity of the pixel was lower than LT, the pixel was rejected, classified as a non-edge pixel and set to a black pixel on the binary image. If the pixel intensity was between the two thresholds (UT and LT), the pixel was classified as an edge only if it was connected to an existing edge pixel. The filter returned binary images in which the white pixels identified as edges were used as an approximation for the real edges of the original images. We defined the sharpness score as the sum of white pixels in the binary image.

2.5.3. Cortico-medullary difference

To evaluate the difference in signal intensity (SI) between the cortex and medulla, ROIs were drawn in a minimum of 3 slices of the anatomic GRE of the healthy volunteers and copied onto the diffusion-weighted images. On each b-value image, regions of interest were placed in the cortex and medulla of the upper, mid and lower poles. In case of severe geometric distortion, some of the ROIs were manually corrected. For each b-value, the cortex and medulla were analyzed separately, and the mean SI was calculated as the mean of all voxels included in ROIs.

2.5.4. ADC

The apparent diffusion coefficient (ADC) was measured on quantitative ADC maps generated using a monoexponential model on a voxel-by-voxel basis according to the following formula:

$$\text{ADC} = \frac{1}{b} \log \left( \frac{S_{\text{voxel}}(b=0)}{S_{\text{voxel}}(b=b_0)} \right)$$

(1)

The ADC values were then averaged in each cortical and medullary ROI as defined above and expressed as mean ± standard deviation.

2.5.5. Qualitative assessment

Finally, all anonymized DW images were presented to a radiologist specialized in uro-radiology (20 years experience) in a blinded and random order for a qualitative visual assessment with regard to the ability to detect small structures, geometric distortions due to susceptibility, cortico-medullary difference and image blurring. A scale ranging from 0 (unacceptable image quality severely deteriorated by artifact) to 4 (artifact-free image without geometric distortions and with high anatomic details) was used to evaluate the overall preference of the radiologist.

2.5.6. Patient images

To further demonstrate the feasibility of the RESOLVE sequence in a clinical setting, the same acquisition protocol was repeated on 10 CKD patients. Selected examples were provided as an illustration of the image quality obtained in a clinical exam. Distortions, sharpness of images and ADC were analyzed as for healthy volunteers. However, the patients’ ADC was compared to the values obtained in volunteers and not correlated with their own clinical data, as this will be the subject of an ongoing clinical study.

2.5.7. Statistical method

Statistical analysis, except for the qualitative assessment, was carried out using one-way analysis of variance (ANOVA) with post-hoc Bonferroni (SPSS software, version 21.0; Chicago, Illinois, USA). The qualitative assessment was analysis using non-parametric Wilcoxon signed-rank test. A value of $p < 0.05$ was taken as statistically significant.

3. Results

3.1. Phantom studies

3.1.1. Geometric distortions

The level of geometric distortions in the phantom is shown in Fig. 1a. The strongest deformation of the phantom borders was observed with the reference EPI, followed by the HR-EPI as quantified by the deviation from the corner of the phantom on the undistorted GRE reference image. The RESOLVE images were characterized by the smallest geometrical deformation among all the sequences. The maximum distance in the phase-encoding direction between the phantom edges of the GRE image and the reference EPI, HR-EPI, RESOLVE images was 1.34 cm, 0.95 cm and 0.47 cm respectively. The geometric distortion was therefore less pronounced for RESOLVE (35% of the reference EPI geometric distortion) than for the HR-EPI (71% of the reference EPI geometric distortion).

3.2. In vivo study

3.2.1. Geometric distortions

Representative in-vivo DW images performed in healthy volunteers, and patients are provided in Fig. 1 (b and c), 2 and 3. Reference EPI images suffered from severe deformations of the kidney border, especially in proximity of the air filled colon. Local deformation of the contours can easily be seen in reference and HR-EPI images. HR-EPI images were less distorted compared to the reference EPI. However, some significant geometric distortions were still visible with this sequence. In all case, the RESOLVE strategy drastically reduced the geometric distortion and the associated heterogeneity of the SI even in regions in close contact to air filled bowel. The whole parenchyma, especially the lower pole of the cortex, was much better delineated on the RESOLVE images than on the two ss-EPI images. As well as these geometric distortions Fig. 3 also illustrates the $b_0$ images of reference EPI, HR-EPI and RESOLVE MR images of a renal allograft in direct contact with the bladder and a renal allograft with visible scar following recurrent episodes of pyelonephritis (eGFR = 57 ml/min/1.73m$^2$) which is more distinct with RESOLVE. Stronger geometric distortions and blurring are clearly visible on both ss-EPI (reference and HR) images compared to RESOLVE images. (See Fig. 2.)

3.2.2. Blurring

The improvement of images resulting in reduced EPI blurring by application of the RESOLVE strategy could also be quantified with the ‘Canny’ filter. The RESOLVE strategy significantly improved the quantitative sharpness score (corresponding to the number of white “edge” pixels, as illustrated in Fig. 4 of RESOLVE images compared to HR-EPI. On average the sharpness score was $348 \pm 150$ pixels for RESOLVE, against $263 \pm 133$ pixels for HR-EPI ($p = 0.007$) and taking the average of the individual improvements, a $56\% \pm 86\%$ higher score was obtained after applying the hysteresis threshold of the ‘Canny’ filter. The bar graph showing the sharpness value of all kidney images (healthy volunteers and patients) is shown in Fig. 5.
In 38/43 cases the sharpness value was higher in RESOLVE compared to HR-EPI (with an average improvement of a 65% ± 89% higher score), indicating a better definition of the renal edges acquired with the RESOLVE sequence. In the 5 volunteers where the sharpness score was higher for HR-EPI than RESOLVE, the difference was always very small (9% ± 9%).

3.2.3. Cortico-medullary difference

The difference in mean SI between the cortex and medulla was improved on the RESOLVE images of the volunteers. This was significant (on b₀ images (p = 0.0025) and b = 300 seconds/mm² images (p = 0.019) with a ratio of mean SI between the cortex and medulla of 1.3 (b₀) and 1.2 (b₂₀₀). On the HR-EPI, only the b₀ images showed a difference (p = 0.0028) for HR-EPI with a ratio of mean SI between the cortex and medulla of 1.1 (b₀). No significant cortico-medullary difference was observed in reference EPI, even on the b₀ images.

3.2.4. ADC

Separate ADC values for the cortex and medulla were calculated. Both HR-EPI and RESOLVE, but not reference EPI, had significant ADC difference between the cortex and medulla of healthy volunteers, as shown in Fig. 6. In healthy volunteers, the mean ADC values (in 10⁻⁶ mm²/s) was for reference EPI 2141 ± 244 in the cortex and 2092 ± 173 in the medulla (p = 0.51), for HR-EPI 2008 ± 254 in the cortex and 1817 ± 224 in the medulla (p < 0.001) and for RESOLVE 1994 ± 246 in the cortex and 1762 ± 238 for RESOLVE in the medulla (p < 0.001). The ADC difference between the cortex and medulla was not statistically different comparing RESOLVE and HR-EPI (p = 0.63 for cortex, p = 0.19 for medulla) and RESOLVE and reference EPI (p = 0.80 for cortex, p = 0.09 for medulla). In patients, the mean ADC values (in 10⁻⁶ mm²/s) measured from the RESOLVE sequence were not different between the cortex (1755 ± 145) and the medulla (1799 ± 163, p = 0.49). Significant statistical ADC difference between healthy volunteers and patients was found in the cortex (p < 0.001) but not in the medulla (p = 0.90).

3.2.5. Qualitative assessment

RESOLVE showed the preferred image quality for all the parameters studied. The mean scores across 20 healthy volunteers for RESOLVE, HR-EPI and reference EPI in terms of geometric distortions, sharpness, and the cortico-medullary difference are shown in Fig. 7. Qualitatively, there was less geometric distortion of the kidney edges in every case (20/20) with RESOLVE vs. HR-EPI (p = 0.02) and vs. reference EPI (p < 10⁻⁸). RESOLVE was considered sharper than reference EPI in all the cases (p < 10⁻⁸) and, in 12/20 cases when comparing RESOLVE and HR-EPI (with an overall significant difference, p = 0.001). RESOLVE was considered just as sharp as HR-EPI in 7/20 cases. For the cortico-medullary contrast, RESOLVE performed better than HR-EPI in 7/20 cases (p = 0.342). Bringing together all qualitative parameters, the RESOLVE score was significantly higher than single-shot EPI score (p = 0.05).

4. Discussion

Our goal was to study the potential of readout-segmented echo-planar imaging with a fivefold segmented k-space acquisition for renal DWI. An improved image quality from the RESOLVE sequence.
over ss-EPI sequences was observed in both healthy volunteers and CKD patients. The respiratory-gated RESOLVE significantly reduced diffusion artifacts and the other hurdles encountered with the use of ss-EPI. Whereas such improvements have already been demonstrated in the brain and breast [8–10,19–21], this is the first report of the use of RESOLVE in the abdominal cavity, which is strongly influenced by susceptibility artifacts resulting from the air/tissue interface in the bowel. In our study, we were able to show an almost complete absence of deformations of the kidney border at proximity of the bowel with the RESOLVE sequence by comparison of the ss-EPI sequence. A

Fig. 2. Comparison of in vivo sequences in healthy volunteers. Coronal MR images of the kidneys in a 26-year-old female. Upper row: b0 images of reference EPI, HR-EPI and RESOLVE. White arrows point to areas of geometric distortions and high signal intensity artifact at the bowel interface. Stronger geometric distortions and blurring are clearly visible on both single-shot SE-EPI (reference and HR) images compared to RESOLVE images. Furthermore, the difference between the cortex and medulla is sharper and better delineated on the RESOLVE images. Lower row shows the respective 4 b-value ADC maps with improved border definition on the RESOLVE image.

Fig. 3. Selective examples of the improvement of RESOLVE in two transplant patients. Coronal b0 images of reference EPI, HR-EPI and RESOLVE MR images of a renal allograft in direct contact with the bladder in a 46-year-old male (upper row) and a renal allograft in 43-year-old female with visible scar following recurrent episodes of pyelonephritis (eGFR = 57 ml/min/1.73m²). Stronger geometric distortions and blurring are clearly visible on both single-shot SE-EPI (reference and HR) images compared to RESOLVE images. Note also the improved visualization of the scars by the RESOLVE sequence in the lower row.
A noteworthy achievement of our work was the high spatial resolution obtained with the RESOLVE sequence that outperformed previous published results at 3 T [22,23]. To compare RESOLVE with ss-EPI with the same spatial resolution, a standard ss-EPI (reference EPI) was set-up with optimized parameters (HR-EPI). Although some significant improvement was obtained with the shorter EPI echo-train length than the reference EPI as a result of the increased bandwidth and acceleration factor, HR-EPI was still less efficient at reducing the susceptibility artifacts than RESOLVE. This could be easily explained by the reduced effective echo-train resulting for the segmented acquisition.

Diffusion measurements are sensitive to differences in hardware (scanner performance) and acquisition parameters such as signal-to-noise and acquisition resolution. Additionally, positioning, alignment, warping, analysis software (segmentation and resectioning), data processing strategies (fit routine), and the absence of consensus in the b-values choice all play a role in the variability of ADC.

Fig. 4. Sharpness evaluation. The first column (a) and (d) shows the $b_0$ images of a healthy kidney using HR-EPI and RESOLVE sequences. (b) and (e) show the gradient images associated to the images (a) and (d). The kidney was better delineated with the RESOLVE strategy, as shown in the gradient images. On these images, a 'Canny' filter with a threshold of 0.4 was applied to evaluate the quality of the edges. The filter returned binary images (c) and (f) representative of the total number of “edge pixels” (white pixels) remaining after the application of the ‘Canny’ filter. The quantitative sharpness score was calculated as the number of white pixels (identifying an edge location). Analyzed regions were selected close around the kidney to avoid artifactual pixels from other organs. The sharpness scores calculated with the binary images were respectively 109 and 421 white pixels for HR-EPI and RESOLVE.

Fig. 5. Sharpness results of all kidneys: healthy and allograft. Bar graph showing the sharpness scores for each individual kidney ($n = 43$) calculated as the sum of white pixels remaining after the use of the ‘Canny filter’. The hysteresis thresholding for the ‘Canny filter’ was 0.16 and 0.4. In 38/43 kidneys, the sharpness score was higher in RESOLVE compared to HR-EPI (on average 56% higher, $p = 0.007$ between the two sequences) demonstrating the improved sharpness of the RESOLVE images.
measurements especially for the cortico-medullary ADC difference [24,25]. In the present study, optimized protocol and hardware on a 3 T MR system allowed observation of the difference in ADC between the cortex and medulla in healthy volunteers. This difference in ADC between the cortex and medulla was in agreement with recent studies on healthy volunteers [26,27]. In transplanted kidneys, the ADC was almost identical in the cortex and the medulla. The lack of a difference between these tissues could be explained by the denervation of the transplanted kidneys as well as the effects of immunosuppressive drugs [14]. An individual analysis of cortico-medullary ADC differentiation was not performed for each patient. Such an analysis would be worthwhile in future work, but is beyond the scope of the current study aiming to compare the image quality of the RESOLVE and ss-EPI protocols. However, we demonstrated that RESOLVE could really be applicable in clinical exams and enhanced significantly the image quality of patients by reducing the blurring and improving the robustness against distortions-related susceptibility artifacts. These results justified further study to evaluate the benefit of RESOLVE in patients.

In the present study, we introduced a new method to quantify and compare the sharpness between MR images based on the “Canny” edge detection algorithm. Such assessment was not performed in the previous published studies comparing RESOLVE and ss-EPI. We highlighted the significant higher sharpness of RESOLVE compared to HR-EPI, which has a similar nominal spatial resolution. Derivation methods developed to detect local intensity variation have been widely used in image processing for edge detection [28]. In cephalometric analysis, an algorithm based on the ‘Canny’ filter has been developed for automatic localization of craniofacial structures [29]. As such, the “Canny” method is often used in image processing, but not specifically for MR image analysis. Normally, MR studies have used sharpness based on profile through organ [30] or qualitative score [31]. The advantage of the ‘Canny’ filter is the quantification of the image sharpness based on the image edge detection method. In addition to a qualitative assessment of the MR images, we were, in this way, able to give a relevant quantitative score for the sharpness that is operator independent. As an additional advantage, our “Canny” edge methodology can easily be transferred to any other type of images comparison.

The main limitation of the RESOLVE sequence is the longer scan time. The increased acquisition time was directly proportional to the number of segments in the acquisition scheme. Although 5 times longer than a single-shot MR diffusion sequence acquisition, the scan time of the RESOLVE sequence (5'63” ± 1'53” measuring on healthy volunteers, against 1'07” ± 3’2” for Reference EPI and 1'11” ± 4’0” for HR-EPI) remained in the range of clinically acceptable MR sequences compared to, for example, respiratory gated coronary MR angiography [32]. In addition, the use of improved acceleration techniques such as compressed sensing could also provide a solution to reduce the acquisition time. Due to the relatively long imaging time of diffusion sequences, displacement of kidneys in the imaging

**Fig. 6.** ADC in healthy volunteers. Box plot illustrating the difference in mean ADC (10^{-6} mm²/s) between the cortex and medulla with the 3 sequences: reference EPI, HR-EPI and RESOLVE. Data were obtained in both kidneys in 20 volunteers. A significant difference in ADC with p < 0.001 (**) is revealed between the cortex and medulla for RESOLVE and HR-EPI but not for reference EPI.

**Fig. 7.** Qualitative assessment in healthy volunteers. Bar graph showing mean scores of the overall imaging quality for visualizing both healthy kidneys separately. The following imaging parameters were under investigation: geometric distortion at susceptibility sites (e.g. proximity of air filled bowel), sharpness and the cortico-medullary contrast. The radiologist defined 0 as unacceptable image quality, severely deteriorated by artifact, and 4 as excellent for an artifact-free image without geometric distortions and with high anatomic details. Reference EPI, HR-EPI and RESOLVE were evaluated for 20 volunteers. p < 0.05 was taken as statistically significant.
plane during the scan is possible. Motion effects can be reduced by means of navigators or respiratory triggers as well as image registration techniques. Several registration techniques have sprung up over recent years to address this artifact in body applications subject to long acquisition time [33-35]. In liver diffusion, registration was applied to increase the robustness in multi-b-value acquisition [36]. A technique similar to the navigator-based RESOLVE reacquisition developed by Porter et al. [7] in head imaging for small motions could also have a potential imaging for extension to renal diffusion.

As a limitation of our study, hydration status, which was not controlled, may explain some of the variability between volunteers [37]. However, this should not compromise the comparison between sequences acquired during the same MR session and hydration status.

Although RESOLVE was superior in terms of image quality to the much shorter HR-EPI, we did not demonstrate in this study a clinical advantage of RESOLVE over HR-EPI in terms of patient’s diagnosis or monitoring. This remains to be investigated by clinical studies. However, from our present result, RESOLVE can already be considered as the first choice of diffusion MR sequences in cases of severe susceptibility artifacts in the abdominal cavity.

5. Conclusions

In conclusion, despite a longer scan time, RESOLVE enhanced significantly the quality of renal diffusion-weighted images by reducing the image distortion and blurring and by improving the difference in SI and ADC between the renal cortex and medulla in healthy volunteers. The performance of the RESOLVE was also demonstrated in CKD patients with a disappearance of the cortico-medullary ADC difference. These improvements justify further clinical studies of the potential of RESOLVE for diffusion MRI.

Acknowledgements

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References

2.2 Publication 2

The goal of this second publication was to validate RESOLVE DWI in a pre-clinical study with well-controlled experimental models of renal fibrosis, before applying this sequence in CKD patients for fibrosis assessment.

Validation of RESOLVE in experimental animal models

Results on the ability of RESOLVE DWI to differentiate between different fibrosis grades using a clinical 3T MR system are presented in the following publication. In parallel, inflammation visualization was investigated on a 14T small animal system for molecular imaging. The contrast agent used was Rienso iron oxide nanoparticles (active agent Ferumoxytol). Ferumoxytol was an intravenous iron preparation (carbohydrate-coated ultra small superparamagnetic iron oxide nanoparticle USPIO) used for the treatment of anemia in adult patients. It was tested as contrast agent to detect macrophages involved in the inflammatory process. MRI can detect iron oxide nanoparticles accumulating in cells, with phagocytic activity such as macrophages. The US Food and Drug Administration and European Union have approved the Rienso for iron iv supplementation. However, due to a death in Switzerland in 2013, Swissmedic withdrew this product from the market and our project to inject patients has been stopped. We focused therefore on the detection of pathology in animal models without contrast agent for further validation of our protocol in CKD patients. Despite this suspension, preliminary results obtained at 14T in collaboration with Dr Nicolas Kunz from the Center for Biomedical Imaging (CIBM EPFL Lausanne, Switzerland) gave knowledge of the rat kidney structure, different from the human (Figure 16).

Figure 16: USPIO-labeled macrophages signal on MR images in the presence of Ferumoxytol in UUO rat model. Ferumoxytol injection was performed 24h before sacrifice for ex vivo scan at 14T. Resolution of MR images was 60 microns isotropic. Iron uptake in the UUO kidney gave a negative contrast on T1-weighted gradient echo and T2-weighted spin echo. In this model, controlateral kidney served as internal control. Photomicrographs of Prussian blue confirmed in vivo USPIO in the renal capsule.
Clinical use of RESOLVE in CKD patients

The protocol developed in small animals, with the RESOLVE sequence, was directly translated to CKD patients DWI. An example of the monoexponential decay of the cortical and medullary signal intensity in two allograft patients, with different level of interstitial fibrosis, is shown in Figure 17.

Figure 17: In the first patient with no fibrosis in histology (A), cortical ADC is higher than medullary ADC, which results in a positive $\Delta$ADC. In the second patient with more than 40% of fibrosis (B), $\Delta$ADC is negative. The increase of the level of cortical fibrosis decreased cortical ADC. At one point, a cortico-medullary inversion occurs and medullary ADC becomes larger than cortical ADC.
By using the absolute cortical ADC, we found a comparable correlation with interstitial fibrosis to those previously measured [39, 54, 90]. The cortico-medullary difference, ∆ADC, allowed an improvement of this correlation. Therefore this paper is important as it goes further than these previous studies by proposing an index to minimize the variability in patients with the same level of fibrosis.

In the following publication, a strong relationship between ∆ADC and the biopsy specimen fibrosis quantification was demonstrated in a homogeneous cohort of 29 kidney allograft patients. ∆ADC outperformed ∆T₁, with a stronger correlation to the percentage of fibrosis (R²=0.64 against R²=0.29, p<0.001). Most importantly, a negative ∆ADC value was measured for all patients harboring more than 40% interstitial fibrosis. This important achievement opened perspectives for an ADC cut-off value to differentiate CKD patients with high or low level of interstitial fibrosis, with 40% fibrosis as the threshold. In addition, the spin-lattice relaxation time (T₁) was investigated in this study. T₁ showed promising results in previous studies on cardiac fibrosis. In the following publication, ADC from RESOLVE DWI and T₁ from T1 Mapping were compared for the first time for renal fibrosis assessment.
New Magnetic Resonance Imaging Index for Renal Fibrosis Assessment: A Comparison between Diffusion-Weighted Imaging and T1 Mapping with Histological Validation

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A need exists to noninvasively assess renal interstitial fibrosis, a common process to all kidney diseases and predictive of renal prognosis. In this translational study, Magnetic Resonance Imaging (MRI) T1 mapping and a new segmented Diffusion-Weighted Imaging (DWI) technique, for Apparent Diffusion Coefficient (ADC), were first compared to renal fibrosis in two well-controlled animal models to assess detection limits. Validation against biopsy was then performed in 33 kidney allograft recipients (KARs). Predictive MRI indices, ΔT1 and ΔADC (defined as the cortico-medullary differences), were compared to histology. In rats, both T1 and ADC correlated well with fibrosis and inflammation showing a difference between normal and diseased kidneys. In KARs, MRI indices were not sensitive to interstitial inflammation. By contrast, ΔADC outperformed ΔT1 with a stronger negative correlation to fibrosis (R² = 0.64 against R² = 0.29 p < 0.001). ΔADC tends to negative values in KARs harboring cortical fibrosis of more than 40%. Using a discriminant analysis method, the ΔADC, as a marker to detect such level of fibrosis or higher, led to a specificity and sensitivity of 100% and 71%, respectively. This new index has potential for noninvasive assessment of fibrosis in the clinical setting.

Kidney Interstitial Fibrosis (IF) is defined as the abnormal deposition of collagen and related proteins in the cortical renal interstitium. IF is a common histological abnormality present in all types of renal disease and is considered to be crucial for the prediction of functional recovery of the kidney and prognosis in most renal diseases1. In kidney allograft recipients (KARs), IF determines allograft prognosis and is used to adapt treatment2-8. IF is currently evaluated by histological analysis of kidney biopsies, which may be complicated by serious bleeding9,10. In addition, these random biopsies are subject to sampling bias and are difficult to perform repeatedly due to potential complications. Finally, there is ongoing debate over the best method to estimate IF histologically, in a reproducible manner, in KARs and chronic kidney diseases (CKD) patients11-13. Diagnostic tools and noninvasive biomarkers for the detection of IF are essential to complement serologic markers and biopsies in order to improve the prognostic and follow-up of KARs, and CKD patients in general. Noninvasive methods such as elastography and fibroscan have been validated for the fibrosis assessment of organs such as the...
Results

Unilateral ureter obstruction in rats induced severe interstitial fibrosis, which was detected by T1 mapping and DWI. Significant difference was found between contralateral (Fig. 1A) and obstructed kidneys (Fig. 1B) in the UUO rat model. As expected, obstructed kidneys displayed tubular dilatation, moderate to severe fibrosis, interstitial inflammation and tubular atrophy as shown in the histological section of a UUO at 2 weeks after animal surgery (Fig. 1B). Kidney cortical fibrosis was quantified by unpolarized Sirius red staining at 1 (n = 7), 2 (n = 6) and 3 (n = 3) weeks and was compared to the non-obstructed, contralateral kidney. Quantification of unpolarized Sirius red staining was significantly higher in the obstructed kidneys compared to the contralateral cortex at all 3 time points (p < 0.05) (Fig. 2A).

In a pilot study to optimize the MRI protocol, traditional single-shot DWI (ss-EPI) images were not suitable for ADC analysis in 14% of whole rat kidneys, compared to images obtained with RESOLVE MRI sequence. Figure 3B shows a typical example of the severe distortion present on a standard ss-EPI image of rat kidney. The parenchyma completely disappeared due to susceptibility artifact and related distortions. On the contrary, RESOLVE DWI improved image quality by reducing image distortion and improving the differentiation of ADC between cortex and medulla. RESOLVE has improved the diagnostic performance of DWI in breast, head and pelvis examinations and similar benefit could be expected in renal patients. However, the performance of RESOLVE for IF assessment in patients has not yet been evaluated. Our goal was, therefore, to compare the performance of Modified Look-Locker Inversion-recovery (MOLLI) T1 mapping and RESOLVE DWI to assess renal IF. First, T1 mapping and RESOLVE DWI protocols were adapted to scan rat models on a clinical 3T MRI scanner. This experimental step was important to evaluate the sensitivity of the MR parameters to detect low levels of fibrosis in well-controlled animal models. These protocols were then applied to KARs undergoing planned biopsy. IF is indeed an important endpoint for adaption of therapy decisions in this population, as well as a marker for allograft prognosis.
weeks, p < 0.05). In summary, MRI sequences with T1 mapping and ADC obtained from DWI were both able to differentiate parenchyma of obstructed kidney from the contralateral control in the UUO model.

Immunologic nephritis induced moderate kidney IF, which was detected by T1 and ADC MRI. To further evaluate the sensitivity of our imaging protocols in a model of milder renal IF, immunologic nephritis was induced by repeated injections of bovine serum albumin (BSA)57. On histology, by unpolarized Sirius red staining, moderate bands of cortical fibrosis with modest foci of interstitial inflammation were present in BSA kidneys (n = 5), compared to sham animals (n = 8) (p < 0.05) as shown in representative histological images (Fig. 1E,F). T1 mapping and DWI of good quality were obtained in all the animals. The different layers of parenchyma were identified by both T1 mapping (shown in Figs 1G and 4C), and the RESOLVE sequence (shown in Figs 1H and 4D). Cortical T1 values showed a trend to be higher in the BSA group compared to the sham group (p = 0.06) (Fig. 2B). The BSA group showed also, a strong positive correlation between cortical T1 and IF (R² = 0.50, p < 0.05) (Fig. 2G). However, when considering only the inflammation score and T1 values, no correlation was found in this population (R² = 0.017, p = 0.76).

Regarding the DWI, the cortical ADC decreased significantly in the BSA group compared to the sham group (p < 0.05) and a strong negative correlation was recorded with increasing IF (R² = 0.55, p < 0.05) (Fig. 2K). In this model also, cortical T1 and ADC performed similarly to detect IF with a significant decrease of the cortical ADC and a significant increase of cortical T1.

In kidney allograft recipients, ADC values showed a stronger correlation than T1 to IF. After validation of our MRI protocol to detect IF in rats using the clinical 3T MR, the same MR protocol was trans- 

4 patients, only T1 values were acquired due to problems with patient compliance as detailed in the flowchart illustrating patient recruitment (Fig. 5).

As gold standard, cortical IF was assessed by automatic unpolarized Sirius red quantification of the biopsied cortex5,38 and also, by classical visual estimation by an experienced pathologist, using Masson trichrome staining. Although the latter is the method used in clinical routine, both methods were investigated in this study and a strong positive correlation between pathologist-assessed Masson trichrome and unpolarized Sirius red quantification for IF assessment was measured (R² = 0.56, p < 0.05) (Fig. 6A). Strong negative correlations were also measured between eGFR39 and IF assessed by Masson trichrome (R² = 0.52, p < 0.001) (Fig. 6B) and by Sirius red (R² = 0.26, p < 0.05) (Fig. 6C). Except in 3 patients with a high level of IF, T1 maps demonstrated a clear cortico-medullary difference as shown in the first row of Fig. 7. The range of T1 values was 1175 to 1527
ms for the cortex and 1327 to 1576 ms for the medulla. T1 was not correlated with eGFR (R² = 0.019 in the cortex (Fig. 6D) and R² = 0.069 in the medulla (Fig. 6E)). To decrease inter-individual variability we calculated the cortico-medullary difference for T1 values (ΔT1), which ranged from −206 to 23 ms. ΔT1 showed a positive correlation with eGFR (R² = 0.22, p < 0.05) (Fig. 6F). No correlation was found between absolute T1 values and IF as assessed either from Masson trichrome (R² = 0.087 in the cortex (Fig. 8A) and R² = 0.012 in the medulla (Fig. 8B)) or from Sirius red (R² = 0.18 in the cortex and R² = 0.016 in the medulla) whereas ΔT1 and IF showed moderate correlations (R² = 0.29, p < 0.05 from Masson trichrome (Fig. 8C) and R² = 0.18, p < 0.05 from Sirius red). A significant but moderate correlation was measured between the Banff scoring system for chronic interstitial lesions (interstitial fibrosis and tubular atrophy, ci+ct) and ΔT1 with R² = 0.27, p = 0.002 (Fig. 8F) but not with the T1 values in either the cortex or medulla alone (R² = 0.13, p < 0.01 respectively (Fig. 8D,E)). Similarly, no correlation was measured when comparing the T1 or ΔT1 and the inflammation as assessed by adding three variables of the Banff pathology score representing tubulo-interstitial inflammation (i+t+i) (R² = 0.06 in the cortex (Fig. 8G), R² = 0.016 in the medulla (Fig. 8H) and R² = 0.09 with the ΔT1 (Fig. 8I)). High image quality was obtained by the RESOLVE sequence, with only few susceptibility artifacts at the edge of the parenchyma (Fig. 7, 2nd row). The ADC values [x10^{-6} mm²/s] had a large range from 1634 to 2816 for the

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**Figure 2.** Histological and MRI results box plot for the UUO and BSA model. The 3 boxes plot illustrate the differences between the control and the model for histological results (A), the mean T1 [ms] (B) and mean ADC [x10^{-6} mm²/s] (C) for UUO and BSA: UUO at time point 1 week (UUO1), 2 weeks (UUO2), 3 weeks (UUO3) and BSA at time point 3 weeks. In UUO, the contralateral kidney served as control. Data were obtained in 29 rats (7 for UUO1, 6 for UUO2, 3 for UUO3, 5 in the BSA group and 8 controls), with p < 0.001 (***) and with p < 0.05 (*). (B) A highly significant difference in T1 was revealed between the control and obstructed kidneys in the UUO model at the three time points but only a trend was observed for the BSA model (p = 0.06). In all case, T1 strongly correlated with the percentage of cortical IF as assessed by Sirius red staining (R² = 0.51 at 1 week (D), R² = 0.43 at 2 weeks (E), R² = 0.98 at 3 weeks (F), p < 0.05) and R² = 0.50, p < 0.05 for the BSA 3 weeks (G). ADC was significantly different between the control and both the UUO model at 2 and 3 weeks (p = 0.013 and p = 0.014) and the BSA model (p = 0.007). The difference in ADC was not significant in the mild UUO model at time point 1 week (p = 0.052) (C). In all cases, ADC inversely correlated with the percentage of cortical IF as assessed by Sirius red staining (R² = 0.24 at 1 week (H), R² = 0.55 at 2 weeks (I), R² = 0.73 at 3 weeks (J), p < 0.05) and R² = 0.55, p < 0.05 for the BSA 3 weeks (K).
cortex and from 1735 to 2620 for the medulla. ADC images demonstrated 3 different contrast combinations: ADC lower in the cortex than medulla (as shown in the healthy kidney and the KAR with 20% IF in Fig. 7), no ADC difference between the cortex and the medulla (as shown in the KAR with 30% IF), and higher ADC in the cortex than the medulla (as shown in the KAR with 80% IF). A moderate negative correlation was found between absolute cortical ADC and IF assessed by Masson trichrome ($R^2 = 0.27$, $p < 0.05$) (Fig. 9A) but not by Sirius red ($R^2 = 0.025$). Cortical ADC and eGFR were not correlated ($R^2 = 0.16$) (Fig. 6G). Medullary ADC was also not correlated with eGFR ($R^2 = 0.025$ (Fig. 6H)) nor with cortical IF ($R^2 = 0.03$ by Masson trichrome (Fig. 9B), $R^2 = 0.02$ from Sirius red)). Given large inter-individual variation, we derived the index of the difference between cortical and medullary ADC ($\Delta$ADC), which ranged from $-193$ to $300 \times 10^{-6}\text{mm}^2/\text{s}$. The $\Delta$ADC index improved significantly the correlation with eGFR ($R^2 = 0.31$, $p < 0.05$ (Fig. 6I)), as well as with IF ($R^2 = 0.64$, $p < 0.05$ by Masson trichrome (Fig. 9C) and $R^2 = 0.37$, $p < 0.05$ by Sirius red). In addition to this strong correlation, a negative

Figure 3. Comparison between single-shot (ss-EPI) and RESOLVE DWI MR sequences in a small animal. Both DWI images were compared to GRE anatomical MR images (A). Standard ss-EPI MR sequences showed severe distortion at the kidney edges (B). In 14% of kidneys, for the ss-EPI images, the parenchyma completely disappeared due to distortions. RESOLVE MR sequences (C) considerably reduced artifact, enabling therefore analysis.

Figure 4. Representative T1 maps and ADC maps of the unilateral ureteral obstruction (UUO) model (A,B) and bovine serum albumin (BSA) nephritis model (C,D). First column, coronal MOLLI T1 maps in the UUO model (A) and in the BSA example (C) followed by coronal ADC map obtained with RESOLVE sequence (B,D). The renal cortex, and the outer and inner medulla were identified on the BSA model and sham, as well as the contralateral unobstructed kidney of the UUO rats. Layers were not distinguished on the left obstructed UUO kidney due to renal parenchyma atrophy.
ΔADC was observed in all patients with more than 40% IF (Fig. 9C). A strong correlation was measured between Banff chronic interstitial lesion gradations for interstitial fibrosis and tubular atrophy (ci and ct) and ΔADC with R² = 0.56, p < 0.001 (Fig. 9F) but not with either the cortex or medulla ADC alone (R² = 0.09, R² < 0.01 respectively) (Fig. 9D,E). No correlation was measured when comparing the ADC and the inflammation scoring in the tubulo-interstitium measured by Banff (i + t + ti) (R² < 0.01 cortex, medulla and ΔADC (Fig. 9G–I)). Based on R² correlation comparison using a Fisher Z-transform test, ΔADC outperformed ΔT1 in assessment of IF assessed by Masson trichrome and by Banff IF/TA (ci + ct) (p < 0.001). Correlation coefficients between ΔADC and IF assessed by Masson trichrome and between ΔADC and Banff IF/TA (ci + ct) were not statistically different (p = 0.641). We further concentrated on the ΔADC to validate a limit of detection for IF with nonparametric Wilcoxon and Bootstrap methods. In the first analysis, by sequentially separating the population into 2 groups: ‘High IF’ and ‘Low IF’ with different possible thresholds, Wilcoxon p-values of all the possible thresholds were computed and the lowest p-value was found for a threshold of 40% (p = 2.6 × 10⁻⁶ (Fig. 10)). By using this level to define KARs as having fibrotic disease or not, and discriminant linear analysis, ΔADC as predictive index provided a sensitivity and specificity of 71 and 100% respectively. Applying the bootstrap method, the accuracy was estimated at 91% with 95% CI [0.77–0.99].

Strong reproducibility of ADC and T1 measurement in the cortex and medulla was found between two readers. For each patient independently, all ICC were superior to 0.91 [95% CI:0.92–0.99] for ADC cortex, ADC medulla and ΔADC and ICC > 0.90 [95% CI:0.63–0.97] for T1 cortex, T1 medulla and ΔT1. Correlation coefficients between the two readers were R² = 0.96 for the ADC evaluation in the cortex, R² = 0.97 in the medulla and R² = 0.95 for the ΔADC (p < 0.05). For T1, correlation coefficients between the two readers were R² = 0.737 (p = 0.001) for the cortex, R² = 0.696 (p = 0.03) for the medulla and R² = 0.178 (p = 0.225) for the ΔT1.

**Discussion**

The main results of this study were as follows: RESOLVE yielded DWI of high quality in both small animals and KARs. In the small animal models, T1 and ADC values were correlated to IF and also to interstitial inflammation and could both efficiently discriminate diseased from healthy kidneys. In patients, adjusting absolute cortical T1 or ADC values to medullary ones by calculating the ΔT1 and ΔADC (difference between cortical and medullary T1 or ADC) improved IF assessment. ΔADC was negative in all allografts harboring more than 40% fibrosis and positive in allografts with less than 40% fibrosis. In KARs, ΔADC outperformed ΔT1 for IF detection.

In animal models, T1 significantly increased in diseased kidneys compared to controls. In contrast to the small animal models, only a moderate correlation between T1 and IF and no correlation between T1 and cellular inflammation parameters were observed in KARs. This discrepancy between small animal models and KARs was surprising and is not fully elucidated. T1 is sensitive to modification of kidney structure induced by fibrosis, but also to other factors such as inflammatory cell infiltration and mainly edema as previously described in more acute settings. Major interstitial inflammation was not a preponderant finding in our KAR biopsies as attested by the Banff scores. Therefore, edema was likely more preeminent in the experimental models than in the more chronic situation of planned biopsies for allograft patients. This may explain the difference between the experimental models and the patients. As it remains very challenging to measure edema on histology, this hypothesis cannot directly be verified.
We observed a clear correlation between IF and ADC values, both in experimental models and in KARs. This was in agreement with previous studies that measured a reduced ADC in vivo in well-controlled animal models of fibrotic kidney compared to healthy kidneys. Currently, 3 studies have investigated the relationship between renal IF and ADC. In a first study, a lower ADC measured in the whole parenchyma was found in CKD patients compared to healthy volunteers. However, ADC in the cortex and medulla was not evaluated separately in this study, as it was not possible to reliably discriminately both these kidney regions in CKD and healthy volunteers’ kidneys. In a second study, ADC correlated with allograft fibrosis, but not cell infiltration in delayed graft function patients at 1 week after transplant. However, the extrapolation of their data to later times after transplantation (such as in our study) is not direct. The confounding effect of acute inflammation on this relationship is not yet well known, even if preliminary data suggested that it could be small. In the third study, Zhao et al. demonstrated a correlation between cortical ADC and IF in CKD. Our present results are in agreement with these findings. Contrary to Zhao et al., who used absolute cortical and medullary ADC values, we introduced in this study a new index, ΔADC. This new index has several advantages to minimize the physiological inter-individual variation and optimize IF assessment in patients. A physiological variation in absolute ADC values was previously reported, even in healthy subjects, between individuals under different conditions of flow and tissue hydration. After water loading, a significant and similar increase of the ADC of 7% in the cortex and 9% in the medulla was measured compared to the baseline. Using ΔADC can minimize these causes of inter-individual variation as the intrinsic variation of ADC is corrected for by normalization from subtraction of the medullary ADC. In addition, the fibrosis changes affect preferentially the cortex. Although the medulla may also display kidney lesions in patients, we observed no correlation between medullary ADC and cortical fibrosis or eGFR in our patient population. This preferential localization of fibrosis also supports the efficiency of the ΔADC. Finally, normalization to the medulla was technically easier and more efficient than to surrounding tissues outside the kidney, since the close proximity of the medulla decreased errors related to B1 and B0 heterogeneity as well as to the coil sensitivity profile. We did not use ΔADC in small animal models, as there was no large inter-individual variation of absolute cortical T1 or ADC observed. In addition, the lack of separation of layers in the obstructed kidney made separate cortex and medulla ROI positioning impossible in the UUO model.

There are several limitations to the present study. Although we acquired 10 b values for the diffusion images, we did not use an IVIM model to fit the data. After preliminary testing, the fit of IVIM model was not sufficiently robust by comparison to the fit of the monoexponential model in agreement with previous observations. We also decided to keep all 10 b values to improve the robustness of the monoexponential fit. The reduction of the number of acquired b values is certainly possible as shown recently in prostate diffusion and could be an
The optimal number of $b$ values for a monoexponential fit in our clinical setting remains to be determined in a further study.

The size of our clinical cohort is relatively small and our population homogeneous. This homogeneity helps with validation in such a cohort, but restricts the knowledge on applicability in a wide range of pathologies. Our patients were KARs undergoing scheduled biopsies and acute pathologies were certainly under-represented. However, we were already able to observe a clear correlation in our sample, strengthening the value of RESOLVE in chronic lesions and specifically in IF evaluation. We distinguished patients with relatively 'low level' of fibrosis from patients with 'high level' of fibrosis across the threshold of 40%. As our population was not uniformly distributed along the linear regression line, we preferred to give accuracy and use the linear discriminant analysis technique instead of using areas under receiver operating characteristic curves. A larger size validation in more diverse, but separate, groups will therefore be needed in the future to generalize this observation to acute and other chronic pathologies, as well as to native kidney diseases. Other limitations include the fact that biopsy as a gold standard is subject to sampling bias whereas MR parameters were measured on multiple slices covering the entire kidney. Additionally, pathological methodology for evaluation of IF is still debated. Finally, our experimental models may not be fully synonymous with KARs patients. Both the UUO and BSA nephritis models were

Figure 7. Representative biopsy and MR images. Morphological MOLLI T1 map used for the positioning of the regions of interest (top row) and ADC maps (lower row) for 3 patients showing the different $\Delta$ADC cases: positive, zero and negative; along with the corresponding fibrosis levels from histology (Masson trichrome staining).
chosen as they are classically used for experimental renal fibrosis, which was the parameter of interest in our study. It should also be emphasized that these models were used as a preliminary validation of the sensitivity of the RESOLVE sequence rather to reproduce chronic pathology expected in kidney transplant.

Although our observation is still preliminary, it already indicates that diffusion MRI with the RESOLVE sequence may specifically identify fibrosis extent in KARs and potentially, in the future, in other kidney patient populations. The correction of inter-individual variability of DWI by calculating the \( \Delta \text{ADC} \) will also render this method more reliable in the clinical setting. Although more work is needed before everyday clinical application, this tool will likely be valuable for the follow-up of patients after therapeutic modifications and to assess the extent of chronic lesions in some patients where biopsy may not be recommended. Finally, this noninvasive method may give us a better assessment of renoprotective drug effects on structural aspects of the kidney, and not only on renal function and/or albuminuria.

In conclusion, we demonstrated that MRI can evaluate IF in experimental models and in kidney allograft recipients. Outperforming T1 mapping, diffusion MRI with the RESOLVE sequence allows differentiation of the cortex and medulla to measure the \( \Delta \text{T1} \), decreasing inter-patient variability and improving correlation to histopathological assessment of IF. Further studies in other types of CKD patients will be needed, but this new technique certainly responds to a need in the clinical setting.

**Methods**

**Experimental animal models.** All experiments were in strict accordance with the principles and guidelines of the Federal Veterinary Office for the Care and Use of Laboratory Animals and were approved by the Canton of Geneva animal experimentation ethics committee (1022/3898/2). All experimental procedures were done under Isoflurane inhalation anesthesia (1.5% O2 and air with 2–3% Isoflurane) and with monitoring during imaging using a respiratory pad (SA Instruments, Stony Brook, NY). Male Wistar rats were used for both models (Janvier, France, weighing 150–175g, aged two months at receipt). In the unilateral ureteral obstruction (UUO) model51, left ureters were visualized through a flank incision and double ligated with 6–0 silk. Animals were imaged and sacrificed at time points of 1 (n = 7), 2 (n = 6) or 3 (n = 3) weeks after ligation and tissue samples from obstructed and contralateral kidneys were collected for histology. The contralateral right kidney served as a control kidney in this model. A second model of interstitial inflammatory nephritis (IN) was induced using bovine serum albumin (BSA) injections in nephrectomized rats37. One week following left-sided nephrectomy, rats were randomly assigned to daily intraperitoneal injections of either 1g BSA in saline (Fraction V, No. A-4503, 96–99% albumin, Sigma Chemical Company, St. Louis, MO) (n = 6 with one deceased rat) or 0.9% saline alone (sham, n = 8). BSA animals were imaged and sacrificed at 3 weeks after the start of the injections. For both models, each

![Figure 8. Correlations between histopathological results (fibrosis estimated by pathological assessment of Masson trichrome (A–C), Banff IF/TA (ci+ct) (D–F) and Banff (i+t+i) (G–I) and T1 values in the cortex and medulla, and \( \Delta \text{T1} \) in 33 KARs. \( \Delta \text{T1} \) (in ms) was calculated as the difference between cortical and medullary T1. In all case, no correlation was found when comparing T1 to histopathological results in the cortex and medulla alone. A moderate correlation was found between \( \Delta \text{T1} \) and the percentage of cortical IF estimated by pathological assessment of Masson trichrome (C) and also, between \( \Delta \text{T1} \) and fibrosis estimated by Banff IF/TA (ci+ct) with respectively (R2 = 0.29 and R2 = 0.27, p < 0.05) (F).](image-url)
time point consisted of separate groups of rats with a single MRI acquisition followed by immediate sacrifice and histologic assessment.

**Kidney Allograft Recipient.** All subjects provided informed consent. The study was approved by the ethics committee at Geneva University Hospitals (CER 11–160) and conducted in accordance with the ethical guidelines set down in the Declaration of Helsinki (1975). The inclusion criteria for our study were patients undergoing a kidney biopsy scheduled for a clinical reason and absence of exclusion criteria. MRI was planned on the same day as the biopsy whenever possible and with a maximum of two weeks delay. Exclusion criteria were the presence of a pacemaker or other MR incompatible devices, pregnancy, claustrophobia, and refusal of patients. From August 2013 to June 2014, 90 KARs underwent scheduled kidney biopsy as part of their medical workup according to the kidney transplantation team at the University Hospital of Geneva. From these 90 patients undergoing biopsies, 40 KARs met the inclusion criteria and gave a written informed consent. Seven candidates were excluded as shown in the flow chart (Fig. 5). In the included patients, biopsy justifications were either systematic follow-up biopsy at 1, 5, 10 or 20 years after transplantation (n = 13), before stopping steroids (n = 3), or indication biopsies (n = 17). The reasons for indication biopsies were: apparition or rise of DSA (donor specific antibodies), suspicion of subacute or chronic renal allograft rejection, subacute increase in serum creatinine levels above the baseline value, apparition of proteinuria or hematuria, control post rejection treatment and control post immunosuppressive therapy change. For practical reasons related to the availability of the MR systems, no patient undergoing emergency biopsy for suspicion of acute rejection was included in our study. Patient characteristics are described in Table 1.

**Histological fibrosis quantification.** Both automated and visual analysis of histological fibrosis was performed. For automated quantification, histological slices with Sirius red staining were scanned on a Mirax 3DHistech microscope (20x objective, calibration 0.232 μm/pixel) and analyzed with Tissue Studio (version 3.60) software (Definiens AG, München, Germany, 2.1.0; Build 27594 × 64 version of Definiens Developer). For IF measurement, slides to be processed were assembled in workspaces for subsequent automatic analysis. Staining information (in general settings for processing) was selected as “IHC dual Brown/Red Chromogene”. The first step was selection of cortical area of the kidney where processing should be applied. This area was selected with manual region of interest (ROI) selection (Draw Polygons). Processing then used “Marker Area Detection” with the following parameters: “Threshold Hematoxylin” = 0.15, “Threshold Brown” = 0.59, “Threshold Red” = 0.11 and “Minimum area” = 10 μm² for human sections. For Sirius red analysis in rats, the parameters were “Threshold Hematoxylin” = 0.07, “Threshold Marker” = 0.45 and “Minimum area” = 10 μm². The selected polygonal ROIs were automatically processed on a Definiens server and results obtained from “Default Export” with all

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Figure 9. Correlations between histopathological results (fibrosis estimated by pathological assessment of Masson trichrome (A–C), Banff IF/TA (ci+ct) (D–F) and Banff (i+t+ti) (G–I) and ADC values in the cortex and medulla, and ΔADC of 29 KARs. ΔADC (in 10⁻⁶ mm²/s) was calculated as the difference between cortical and medullary ADC. Cortical IF (estimated by pathological assessment of Masson trichrome) was moderately correlated with cortical ADC (A) but strongly with ΔADC (R² = 0.64, p < 0.001) (C). All patients with more than 40% IF presented a negative ΔADC. A strong negative correlation was also measured with Banff IF/TA (ci+ct), whereas no correlation with interstitial inflammation assessed by Banff (i+t+ti) was measured (G–I).
parameters. The parameters analyzed and reported in paper correspond to area of red marker area [μm] divided by total area of the selected ROI [μm], reported as a percentage. For the visual assessment of inflammation in experimental animals, sections were graded from 0 to 3 for inflammatory infiltrate, separately and in a blinded fashion by two experienced nephrologists. The mean value was then conserved. In patients, in addition to the automated analysis of the Sirius red staining, fibrosis and interstitial inflammation was assessed by an experienced clinical pathologist from the Masson trichrome and HE staining and graded in the Banff scoring system40,41 as well as giving percentage for interstitial fibrosis. Histopathological changes including tubulitis (‘t’ score), interstitial inflammation (‘i’ score) and total interstitial inflammation (‘ti’ score) were added to define the tubule-interstitial inflammation Banff score (i + t + ti). Moreover, interstitial fibrosis (‘ci’ score) and tubular atrophy (‘ct’ score) were used to define the BANFF IF/TA (ci + ct) score. In one patient the ci and ct were not graded because the histological material was too small.

**MR imaging.** MRI was carried out on a Siemens Magnetom Trio (Tim system) 3T clinical scanner (Siemens AG, Erlangen, Germany). Pseudo-coronal T1 maps were acquired with the Modified Look-Locker Inversion recovery (MOLLI) pulse sequence17. For DWI, both a conventional single-shot diffusion-weighted imaging sequence (ss-EPI) and ‘Readout Segmentation Of Long Variable Echo train’ (RESOLVE) sequence52 were acquired with the same resolution, shimming, GRAPPA factor and b-values. All parameters are given in Table 2. The optimized single-shot DWI with the same resolution and b values was attempted, but as the images were not of analyzable quality they are not reported in the table for simplicity.

**Figure 10.** Evaluation of the limit at 40% IF for the definition of “Low Fibrosis” versus “High Fibrosis” detectable using the ΔADC index. The percentage of IF was defined as binary factor using 2 groups: ‘Low Fibrosis’ and ‘High Fibrosis’. (A) Wilcoxon p-values between ‘Low Fibrosis’ and ‘High Fibrosis’ groups were computed for IF thresholds between 10% and 70% by increment of 10% (with zoom shown for 30% to 50%). The best separation between groups “Low Fibrosis” and “High Fibrosis” was found at a limit of 40% with the lowest p-value computed (p = 2.6 × 10⁻⁶). The other separating limits were 10% (p = 2.0 × 10⁻²), 20% (p = 9.4 × 10⁻⁵), 30% (p = 3.2 × 10⁻⁴), 40% (p = 2.6 × 10⁻⁴), 50% (p = 1.7 × 10⁻⁴), 60% (p = 8.4 × 10⁻⁵), 70% (p = 3.4 × 10⁻³). Due to the large p-value the 10% threshold is not included on the plot to keep the vertical scale of the remaining points visible. (B) Classification of each ΔADC with this limit at 40% into separate groups as ‘Low Fibrosis’ and ‘High Fibrosis’ groups. At this level of IF, KARs with positive ΔADC and KARs with negative ΔADC can be separated without overlap between the interquartile range (boxes). (C,D) The accuracy of the limit of 40% IF to separate ‘Low Fibrosis’ to ‘High Fibrosis’ groups according to the ΔADC was 91% with 95% CI [0.77−0.99]. Bootstrap values were shifted close to 1.0 at a level of 40% (D) compared to the accuracy distribution at 30% (C), indicating that 40% IF was more accurate to separate “Low” to “High” fibrosis.
MRI image analysis. MRI image examinations were performed blinded to all clinical parameters and histologic results in each patient. In experimental animals, blinded analysis was not possible in the UUO model due to clear morphological differences, but was performed in the BSA model. MR images were analyzed on an external workstation (OsiriX 5.5.2). The mean T1 or ADC was calculated as the mean of all pixels included in

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<th>All Patients (n = 33)</th>
<th>Patients with RESOLVE Sequence (n = 29)</th>
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<tr>
<td>Age of transplant (years)</td>
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<tr>
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<td>Sirius Red automatized</td>
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<tr>
<td>i = interstitial inflammation</td>
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<tr>
<td>t = tubulitis</td>
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<td>ti = total interstitial inflammation</td>
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<td>g = glomerulitis</td>
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<tr>
<td>ci = interstitial fibrosis</td>
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<td>ct = tubular atrophy</td>
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<tr>
<td>Tubulo-interstitial inflammation (i + 1 + ti)</td>
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Table 1. Characteristics of clinical and laboratory patient data.
ROIs ± standard deviation from multiple ROIs. ADC was measured on quantitative ADC maps generated using a monoexponential model on a pixel-by-pixel basis.

Experimental animal models. A single ROI was placed exclusively in the renal cortex of all BSA animals and the control in the UUO model. The obstructed UUO kidney no longer showed a differentiation between the cortex and medulla. In this group, care was taken to avoid the dilated cavity and to remain in the solid part of kidney containing a mixture of cortex and medulla. Pearson’s correlations between MRI and histological parameters were carried out per group due to possible staining variations. Box plots and one-way analysis of variance (ANOVA) with post-hoc Bonferroni (SPSS 21.0) were used to assess statistical differences (p < 0.05 was statistically significant).

KARs. Multiple ROIs were placed in the cortex (n = 11 ± 3) and in the medulla (n = 19 ± 6) of the central and consecutive slices of each kidney. The SI of all these ROI was averaged to provide a single value for either the cortex or the medulla. Mean size of each individual ROI was 1.2 cm² ± 0.1 cm² for the cortex with the range size 0.6–2.7 and 0.4 cm² ± 0.04 cm² for the medulla with the range size 0.2–0.7. To reduce T1 and ADC inter-individual variability in patients, indices ΔT1 and ΔADC were calculated as: ΔT1 = T1cortex − T1medulla and ΔADC = ADCcortex − ADCmedulla. Correlations were considered significant when p < 0.05. Correlation coefficient comparison was performed using the Fisher Z-transform (http://www.fon.hum.uva.nl/Service/Statistics/Two_Correlations.html). Two observers also performed inter-observer agreement for the T1 and ADC values measured in the cortex and medulla, as well as ΔT1 and ΔADC. Ten KARs were chosen randomly and inter-observer reproducibility was calculated using Pearson’s correlations and Intra-class Correlation Coefficient (ICC) using one-way random single measures.

MRI and biopsy data were finally analyzed in order to define the best IF threshold detectable by DWI. IF was defined as a binary factor determining the presence or absence of fibrosis using thresholds from 10% to 70% in increments of 10%. After the IF percentage was transformed into a binary factor “high IF” or “low IF” (above or below a predefined fibrosis threshold), a non-parametric Wilcoxon test was used to compute the p-value between the both groups. The fibrosis threshold was selected at the level where the Wilcoxon test was the most significant. In a further analysis, a linear discriminant analysis allowing the classification of each ΔADC measure as normal or pathologic was performed to compute sensitivity and specificity of the DWI for the selected level of fibrosis defined previously by the Wilcoxon test. The accuracy was obtained using a bootstrapping method. Such resampling with 1000 bootstrap samples provided a nonparametric distribution of the accuracy and an estimation of the performance measure as a mean with confidence intervals (using software, R 3.1.1).

Table 2. MRI parameters for MOLLI T1 mapping and RESOLVE diffusion weighted imaging. Only the coils and the resolution were different between the experimental and clinical protocols.

<table>
<thead>
<tr>
<th>MRI Sequence Parameters</th>
<th>MOLLI</th>
<th>RESOLVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- In KARs</td>
<td>Phased-array abdominal &amp; spine</td>
<td>Phased-array abdominal &amp; spine</td>
</tr>
<tr>
<td>- In rats</td>
<td>Wrist</td>
<td>Wrist</td>
</tr>
<tr>
<td>TR/TE [ms]</td>
<td>711/1.09</td>
<td>2200/68</td>
</tr>
<tr>
<td>Acquisition time</td>
<td>15 ± 3</td>
<td>9.47 ± 4.1</td>
</tr>
<tr>
<td>Resolution [mm³]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- In KARs</td>
<td>2 × 2 × 5</td>
<td>2 × 2 × 5</td>
</tr>
<tr>
<td>- In rats</td>
<td>0.7 × 1.1 × 3.5</td>
<td>1.2 × 1.2 × 2.2</td>
</tr>
<tr>
<td>Echo spacing [ms]</td>
<td>2.6</td>
<td>0.32</td>
</tr>
<tr>
<td>Flip angle [°]</td>
<td>35</td>
<td>180</td>
</tr>
<tr>
<td>TI (inversion time) [ms]</td>
<td>161, 241, 321</td>
<td>No</td>
</tr>
<tr>
<td>Phase partial Fourier</td>
<td>6/8</td>
<td>Off</td>
</tr>
<tr>
<td>Number of shots per slice</td>
<td>No</td>
<td>5</td>
</tr>
<tr>
<td>GRAPPA factor</td>
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<td>3</td>
</tr>
<tr>
<td>Number of signal averages</td>
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<tr>
<td>Gradients for b values &gt; 0</td>
<td>No</td>
<td>3 orthogonal directions</td>
</tr>
<tr>
<td>b-values [s/mm³]</td>
<td>No</td>
<td>0, 10, 20, 40, 60, 150, 300, 500, 700, 900</td>
</tr>
</tbody>
</table>

References


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This work was supported by grants from the Clinical Research Center of the Medicine Faculty of Geneva University and Geneva University Hospital, as well as the Leenaards and Louis-Jeantet foundations, the Centre for Biomedical Imaging (CIBM), and the Swiss National Foundation (grant 32003B_159714).

**Author Contributions**
I.F. wrote the manuscript with contributions from L.A.C., S.d.S. and J.-P.V. All authors reviewed the manuscript. I.F. worked on the MRI with L.A.C. and the statistics with T.d.P. and L.B. recruited patients and contributed to figures, S.M. and K.H. analyzed patient biopsies, C.V. made the small animal model, I.F., P.-Y.M. and S.d.S., L.A.C. and J.-P.V. designed the study and supervised the whole work. I.F. and L.A.C. contributed equally to this work as first authors. S.d.S. and J.-P.V. contributed equally as last authors.

**Additional Information**

**Competing financial interests:** The authors declare no competing financial interests.

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Supplementary Material Publication 2
2.2.1 Supplementary Publication 2

T1 Mapping and Diffusion-Weighted Imaging in a Multiparametric MR study

Manuscript in preparation for publication

Multiparametric studies are beginning to emerge for renal disease assessment. However these studies investigated each MR parameter independently comparing the MR sequences but did not combine multiple parameters in a single statistic model. In this supplementary data, ∆ADC and ∆T1 were combined in a single statistic with the hypothesis that used together the detection of interstitial fibrosis can be improved.

This work received the ISMRM Cum Laude Merit Award at the ISMRM 24th Annual Meeting in 2016.

The cortico-medullary differences, ∆T1 and ∆ADC, of 31 CKD patients scheduled for biopsy were measured at 3T with a resolution of 2×2×5mm³. Pearson’s correlations with \( R^2 \) were performed to correlate separately ∆T1 and ∆ADC to the extent of interstitial fibrosis. A three-dimensional plot of the Multiple Linear Regression (MLR) model relating interstitial fibrosis to both MR parameters simultaneously was computed and \( R^2 \) adjusted was calculated. An increase of ∆T1 (\( R^2=0.29, p<0.001 \)) and a decrease of ∆ADC (\( R^2=0.68, p<0.001 \)) were measured with increasing interstitial fibrosis. ∆T1 and ∆ADC did not correlate with each other (\( R^2=0.14, p<0.05 \)), signifying that these two MR parameters are complementary in fibrosis assessment. The correlation with interstitial fibrosis was improved by associating ∆T1 and ∆ADC together (\( R^2_{\text{adjusted}}=0.74, p<0.001 \)). The methodology presented in this study could easily be extended to other fields of multiparametric imaging.
Multiple Linear Regression analysis of T1 Mapping and Readout-Segmented Echo-Planar Diffusion-Weighted Magnetic Resonance Imaging for Predicting Kidney Fibrosis

Introduction

The understanding of major pathologies requires the inclusion of several biomarkers to take into account the disease complexity. A pooling strategy is, especially when the diseases involve different processes, not adequately characterized by a single factor. The inclusion of multiple experimental and confounding effects is widely used in various medical research areas such as fMRI (1) or psychiatry with, for example, depression, which requires multivariate approaches rather than modelling each outcome separately to provide better patient care (2). The Multiple Linear Regression (MLR) allows us to analyse overall contributions (3, 4). MLR models the relationship between multiple independent explanatory variables, or predictors, and a response variable. Multiple factors that affect a single outcome can thus be combined to enhance the predictive power (5). In our case, we applied MLR to non-invasively assess renal interstitial fibrosis by Magnetic Resonance (MR) imaging (MRI). MLR is particularly well suited for interstitial fibrosis assessment as histological fibrosis quantification gave a continuous range of fibrosis percentage (5). MRI is emerging as a promising non-invasive medical tool to assess various pathologies, currently evaluated by biopsy. Acquiring multiple MR sequences in a MRI protocol is already currently applied and allows investigation of different MR contrast induced by the disease. However, all these cross-sectional MRI studies investigated each MR parameter independently comparing the MR sequences but do not combine multiple parameters in a single statistic to improve the linear regression. Indeed, the data collection was traditionally
analysed by relating each of the predictor variables, one at a time, to the single response variable with the use of a series of simple linear regressions. For examples, in oncology, the combination of T2-Weighted and Diffusion-Weighted Imaging (DWI) has shown to be more reliable than any other diagnostic procedure for differentiating benign and malignant prostate cancer with the presence of the lesions on all MR images (6, 7). Also, the use of several MR contrasts facilitates and confirms the diagnosis imaging in kidney evaluation for differentiating subtypes of renal tumour (8-10). In Chronic Kidney Disease (CKD) assessment, independent analysis of renal perfusion, Apparent Diffusion Coefficient (ADC) from DWI, T2 and T1 relaxation times showed in kidney transplantation in mice that renal perfusion and ADC negatively correlated with infiltration and fibrosis whereas T1 and T2 were positively correlated (11). These studies are limited by the fact that a simple regression cannot take into account the simultaneous effects of multiple predictors on a response (5). For this reason, in this multi-parametric MR study, we investigated, the two most promising MR sequences for renal interstitial fibrosis assessment, T1 Mapping (12-14) and readout-segmented DWI (RESOLVE (15, 16)), with a 2-dimensional data analysis. Interstitial fibrosis is a complex and multifactorial process that was previously characterized in renal allograft with ADC from DWI and T1 relaxation time from T1 Mapping (17, 18) as separately assessed parameters. A strong negative correlation between ADC and interstitial fibrosis was measured in small animals and human studies (17-20). The restriction of interstitial space because of the profligacy of collagen deposition is directly responsible of a reduction of the extracellular space (21, 22). The ADC parameter is sensitive to this reduction of the interstitial space and the reduction of the interstitium, which both lead to a decrease of the diffusion of water molecules and therefore a decrease in ADC. Whereas, T1 value, another tissue-specific parameter, increased with increasing diffuse myocardial fibrosis (23) and renal interstitial fibrosis (11, 17). T1 depends on intracellular, as well as
extracellular components leading to confounding effects that can influence T1 values. T1 values increase with several factors, such as excess water in oedema (24) and protein deposition such as amyloidosis (25). Our aim was to determine, using an MLR model, if these two MR parameters, ADC and T1, yield competing or complementary data. For that, the sensitivity of the two MRI sequences, T1 Mapping and RESOLVE, was first compared with one another, and independently evaluated against interstitial fibrosis of CKD patients from their renal biopsy. Surgical biopsy specimens from Masson trichrome staining served as gold standard. The two MR parameters were then associated in a single statistic with the hypothesis that MLR can be applied to improve the detection of interstitial fibrosis.

**Materials and Methods**

Part of the data used for this study was obtained from retrospective cohort study (17), which has been approved by the local ethics committee (CER 11-160) and was conducted in accordance with the ethical guidelines set down in the Declaration of Helsinki (1975). Thirty-one CKD patients (21 male, 10 female; age 53 ± 14), scheduled for renal biopsy as part of their medical workup, were included after written informed consent. Interstitial fibrosis was quantified by an experienced clinical pathologist and graded as a percentage from Masson trichrome staining. MR imaging used a 3T MR Siemens Magnetom Trio Tim system. Sequence parameters are summarized in table 1 for the motion corrected Modified Look-Locker Inversion recovery (MOLLI) T1 mapping (WIP 388) and the respiratory-gated implementation of Readout Segmentation of Long Variable Echo train (RESOLVE) DWI.
<table>
<thead>
<tr>
<th>MRI sequence Parameters</th>
<th>MOLLI T1 Mapping</th>
<th>RESOLVE DWI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coils</td>
<td>Phased-array</td>
<td>Phased-array</td>
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<tr>
<td></td>
<td>Abdominal &amp; Spine</td>
<td>Abdominal &amp; Spine</td>
</tr>
<tr>
<td>Slices orientation</td>
<td>6 coronal-oblique slices</td>
<td>6 coronal-oblique slices</td>
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<tr>
<td>TR [ms]</td>
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<td>2200</td>
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<tr>
<td>TE [ms]</td>
<td>1.09</td>
<td>68</td>
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<td>Resolution [mm³]</td>
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<tr>
<td>Phase partial Fourier</td>
<td>6/8</td>
<td>No</td>
</tr>
<tr>
<td>Number of readout segments</td>
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<td>5</td>
</tr>
<tr>
<td>Number of signal acquisition</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 1: MRI parameters for MOLLI T1 Mapping and RESOLVE DWI

Post processing was performed blinded to histopathological diagnosis. Regions-Of-Interest (ROIs) were placed for individual analysis of both the cortex and medulla as previously (17), and the resulting values were used to calculate the cortico-medullary differences $\Delta T1$ and $\Delta ADC$ (Apparent Diffusion Coefficient from RESOLVE). Pearson correlations were performed to compare $\Delta T1$ to $\Delta ADC$ as well as, $\Delta T1$ and $\Delta ADC$ to the extent of interstitial fibrosis. An MLR model was used to assess with $\Delta T1$ and $\Delta ADC$ as MR predictor variables.
\(X_{i1}\) and \(X_{i2}\) of interstitial fibrosis \((y_i)\) according to the following general equation

\[
y_i = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \cdots + \beta_{p-1} x_{i,p-1} + \varepsilon_i
\]

where \(\varepsilon_i \sim N(0, \sigma^2)\) independently distributed, \(\beta_i (i=0,2,\ldots, k)\) are the regression slope parameters and \(\varepsilon\) is the residual errors distribution (26). To evaluate the performance of the MLR model, \(R^2_{\text{adjusted}}\) was computed for the combined correlation of \(\Delta T1\) and \(\Delta ADC\) to the extent of renal fibrosis. The evaluation of the MLR model was done via the four standard regression diagnostic plots (residuals versus fitted values, normal Quantile-Quantile plot, scale-location plot, residuals versus leverage plot with the Cook’s distance) that investigated visually the quality of the model by graphical residuals analysis. The observed residual errors should reflect the properties assumed for the unknown true error terms, such that residual errors \(\varepsilon\) were independent normal random variables with zero mean and constant variance. In addition, the absence of influential outliers in the linear regression analysis was verified with the Cook’s distance. Fit residues were plotted in ordinate axis.

**Results**

MR image quality was adequate for diagnosis in all cases and no patients were excluded from the analysis. An example of coronal MR images obtained with MOLLI T1 Mapping and ADC maps from the RESOLVE sequence are shown in Figure 1 for 2 allograft patients.
As shown in these two examples, an increase of $\Delta T1$ and a decrease of $\Delta ADC$ were associated with an increase in renal interstitial fibrosis defined from Masson trichrome staining. In the whole CKD population (including interstitial fibrosis up to 80%) the $\Delta T1$
range of values was between -206 and 23 ms with a mean ΔT1 of -137 ± 39 ms and, the ΔADC range of values was -193 to 300 ×10^{-6} \text{mm}^2/\text{s} with a mean ΔADC of 68 ± 102 ×10^{-6} \text{mm}^2/\text{s}. ΔT1 and ΔADC both correlated with renal interstitial fibrosis with a moderate positive correlation when comparing ΔT1 and interstitial fibrosis (R^2=0.29 \ p<0.001) and, a stronger negative correlation between ΔADC and interstitial fibrosis (R^2=0.68 \ p<0.001) in this population. However, as shown in Figure 2, ΔT1 and ΔADC did not correlate with each other (R^2=0.14 \ p<0.05), suggesting that these two MR parameters are complementary in fibrosis assessment.

![Figure 2: Weak correlation between ΔT1 and ΔADC with R^2=0.14, p<0.05 (n=31).](image)

Both MR parameters probed independent effects linked to interstitial fibrosis and could be combined to create the three-dimensional plot shown in Figure 3. In Figure 3, a correlation plane relating renal interstitial fibrosis to both ΔT1 and ΔADC was created with simultaneous consideration of both MR predictors. In complement to the conclusions we
drew from separate simple regressions of $\Delta T1$ and $\Delta ADC$ against percentage of fibrosis, the multiple regression equation, with the slope coordinate of the correlation plane of 0.12 for $\Delta T1$ and -0.138 for the $\Delta ADC$, in order to estimate the additive influences of fibrosis on both MR parameters.

**Figure 3:** $\Delta T1$ and $\Delta ADC$ both correlated with renal interstitial fibrosis as shown in the two plots on the left. A correlation plane combining $\Delta T1$, $\Delta ADC$ and interstitial fibrosis is shown on the right ($N=31$).

The correlation between MR and histological interstitial fibrosis was improved when both MR parameters were combined together to correlate against the percentage of fibrosis ($R^2_{\text{adjusted}}=0.74$, $p<0.001$). We verified that residuals associated to our MLR model are normally distributed and have equal variance across all the predictors’ data space to ensure
robustness of the model. Diagnostic plots in Figure 4 show validation of the global quality of the model through the assumptions made on residues.

Figure 4: Diagnostic plots from the MLR regression of renal interstitial fibrosis on $\Delta$ADC and $\Delta$T1 MR parameters. Standardized residuals are rescaled so that they have a mean of zero and a variance of one. (A) shows a random scatter of points approximately equally spread above and below the horizontal line at 0, meaning that assumption of linearity is reasonable. The residuals distribution against those of a sample of independent normal follows a straight line (B), indicating that residuals are normally distributed. Homoscedasticity (constant variance assumption) was verified in (C) with the absence of a particular shape, and the red line being relatively straight. (D) shows the large Cook’s distance (i.e > 0.5) with no influential outliers that affect the regression plan (D).
All the assumptions of the regression appeared to be upheld. Residuals versus fitted values are shown in Figure 4 A. In our model, a slight parabola was observed, but no distinctive pattern in the cloud of points (residuals were distributed randomly around the 0 line), giving a reasonable indication of a linear relationship between interstitial fibrosis and the MRI variables. The normal probability plot of residuals (Quantile-Quantile plot) (Figure 4 B) followed roughly a linear diagonal, meaning that the error terms were normally distributed. The square of standardized residuals versus fitted values showed that equal variance assumption was met with the spread points distributed randomly along a horizontal line as shown in Figure 4 C. Finally, residuals versus leverage plot confirmed the absence of influential data points in the regression (Figure 4D). No outlying value was present at the upper and lower right corners outside the Cook’s distance limits (dashed line).

Discussion

The novelty of this multiparametric study lies in using a combined statistic, and not only the use of multiple separate correlations to assess interstitial fibrosis. The two MR parameters used have been proven to be sensitive to different pathological processes involved in renal interstitial fibrosis. In our study, the MLR is proposed in order to improve the detection of this fibrosis. A previous study used ΔADC to minimize inter-individual variation compared to cortical ADC used alone. This study showed that ΔADC strongly correlated to interstitial fibrosis and, outperformed ΔT1 for renal fibrosis assessment (17). However, the specificity of ADC for fibrosis/CKD is still limited as this parameter also decreases in other parenchymal diseases, which lead to a restriction of diffusion (27, 28). The presence of confounding factors that can alter the detection of interstitial fibrosis, by also reducing the water molecules mobility in tissue, was minimize by adding the T1 relaxation time. We hypothesized that T1 values could detect underlying effects associated indirectly with
interstitial fibrosis and could show a better discrimination of confounding factors in our CKD cohort. Indeed, another major pathological process that can accelerate the progression of CKD comes from endothelial dysfunction. Endothelial dysfunctions, such as renal tissue hypoxia, increase vascular permeability, inflammation, vasoconstriction and capillary rarefaction. These processes facilitate the progression of albumin in renal tissue, primarily the renal medulla, and are often associated with renal interstitial fibrosis (29). T1 is sensitive to the presence of albumin (30), hyperoxia and changes that influence blood volume in tissue (31).

A limitation of this study is the relatively small size of the cohort. In particular, patients with a high level of interstitial fibrosis are missing. This will be the subject of another study in a larger cohort. In conclusion, this study showed that MLR analysis, with the inclusion of ΔADC and ΔT1 in the model to assess the adjusted combined influence of both MR parameters, and improved the detection renal interstitial fibrosis.
REFERENCE


2.3 Publication 3

Diagnostic interest of RESOLVE compared to ss-EPI for renal fibrosis assessment

This publication looked at the diagnostic performance of RESOLVE, compared to ss-EPI, for kidney fibrosis assessment, with histopathology as a gold standard.

In the first publication of this thesis [28], we found that the RESOLVE sequence enhanced significantly the quality of renal DWI. However, the diagnostic advantage of RESOLVE compared to ss-EPI was unknown for fibrosis assessment. This was important to assess, regarding the increased acquisition time required by the RESOLVE sequence.

A homemade gel phantom was used for the comparison of both DW sequences in stable and reproducible conditions. In addition to the monoexponential model, the IVIM model (in the first part of the introduction chapter) was investigated with the biexponential fitting of the DW data. The goal was to evaluate if quantification of the pseudo perfusion could bring additional biomarkers for renal fibrosis assessment.

The main conclusion was, even though less than 3% variability was measured between ADCs (RESOLVE and ss-EPI DWI) in the phantom, a significant difference was measured in healthy volunteers. The improvement achieved with RESOLVE was not strictly limited to the image quality. The cortico-medullary difference $\Delta$ADC from RESOLVE showed a better correlation with interstitial fibrosis than $\Delta$ADC from the traditional ss-EPI DWI used in clinical routine. This important confirmation motivated us to perform an external validation study of the preliminary data described above, in a large cohort of patients (including allograft and native kidneys). The project is still ongoing with currently more than 150 CKD patients recruited and analyzed. Regarding $D^*$ and f from the biexponential fitting, these parameters did not correlate with interstitial fibrosis in our population.
Comparison of Readout-Segmented and Conventional Single-Shot for Echo-Planar Diffusion-Weighted Imaging in the Assessment of Kidney Interstitial Fibrosis

Iris Friedli, MS,1* Lindsey Alexandra Crowe, PhD,1 Thomas de Perrot, MD,1 Lena Berchtold, MD,2 Pierre-Yves Martin, MD,2 Sophie de Seigneux, MD, PhD,2 and Jean-Paul Vallée, MD, PhD1

Purpose: To compare readout-segmented echo-planar imaging (EPI) (RESOLVE) to single-shot EPI (ss-EPI) diffusion-weighted imaging (DWI) for the assessment of renal interstitial fibrosis.

Materials and Methods: A phantom, eight healthy volunteers (under 30 years to avoid age-fibrosis related) and 27 chronic kidney disease (CKD) patients (scheduled for kidney biopsy) were scanned (at 3T) with ss-EPI and 5-shot RESOLVE DWI (resolution: $2 \times 2 \times 5$ mm$^3$, 10 b-values). The cortico-medullary difference for each DW parameter from a monoexponential fit ($D_{ADC}$) or, segmented biexponential fit ($D_{D}$, $D_{D*}$, $D_{Fp}$) were compared between both sequences. A fibrosis threshold of 40% was defined to separate all 35 subjects into low and high fibrosis groups. The linear relationship between DW parameters and percentage fibrosis (up to 80%) from Masson trichrome was assessed with the Pearson product-moment correlation coefficient. Fisher Z-transform was used for $R^2$ correlation comparison.

Results: A coefficient of variation between ADCs of 3% was measured between both sequences in the phantom. In healthy volunteers, no significant difference was measured for all DW parameters. Both sequences separated low to high level of fibrosis with a significant decrease of $D_{ADC}$ (RESOLVE $P = 3.1 \times 10^{-6}$, ss-EPI $P = 0.003$) and $D$ (RESOLVE $P = 8.2 \times 10^{-6}$, ss-EPI $P = 0.02$) in the high level of fibrosis. However, RESOLVE $\Delta ADC$ had a stronger negative correlation ($P = 0.04$ for $R^2$ comparison) with fibrosis than ss-EPI $\Delta ADC$ (RESOLVE $R^2 = 0.65$, $P = 5.9 \times 10^{-9}$, ss-EPI $R^2 = 0.29$, $P = 8.9 \times 10^{-4}$). $D$ (RESOLVE) was correlated (moderately) with fibrosis ($R^2 = 0.29$, $P = 9.2 \times 10^{-4}$); however, $D^*$ and $\Delta F_p$ did not show, in our population, a significant correlation with interstitial fibrosis ($0.01 < R^2 < 0.08$).

Conclusion: $\Delta ADC$ derived from both sequences correlated with fibrosis. $\Delta ADC$ from RESOLVE showed better correlation with fibrosis than $\Delta ADC$ from ss-EPI and therefore has potential to monitor CKD.

Level of Evidence: 1

Chronic kidney disease (CKD) is defined as an alteration of kidney structure and/or function lasting for more than 3 months. The prevalence of CKD is high, with about 1 in 10 adults suffering from some degree of CKD. The level of kidney cortical interstitial fibrosis (from now on referred to as interstitial fibrosis) is recognized as an indicator of impaired renal function and is also predictive of a more serious evolution in most kidney diseases. Renal interstitial fibrosis is characterized by changes in the interstitial space, such as a deposition of extracellular collagen and the destruction of renal tubules and interstitial capillaries. Currently, the gold standard to evaluate these structural alterations is kidney biopsy. However, this procedure is difficult to perform repeatedly and is associated with a risk of hemorrhage as well as sampling bias. There is currently no validated noninvasive method to diagnose and monitor renal interstitial fibrosis.

Magnetic resonance imaging (MRI) with diffusion-weighted imaging (DWI) is emerging as a tool to assess renal...
interstitial fibrosis. DWI enables assessment of water molecule mobility via quantification of parameters such as the apparent diffusion coefficient (ADC), the most widely used, from a monoexponential fit, as well as pure diffusion (D), perfusion-induced pseudodiffusion (D*), and perfusion fraction (Fp) coefficients from a biexponential fit. ADC from DWI correlates with interstitial fibrosis in CKD patients and animal models and carries potential to change the diagnostic workup and follow-up of CKD patients. However, ADC measurements are technically challenging and highly variable. Generally, renal DWI is performed using a single-shot k-space trajectory, namely, single-shot echo-planar imaging (ss-EPI), which suffers from artifacts due to a long echo train length (ETL). Off-resonance and $T_2^*$/C2 blurring artifacts associated with the long ETL can be reduced by increasing the receiver bandwidth and by the use of parallel imaging techniques such as generalized autocalibrating partially parallel acquisitions (GRAPPA) to reduce the echo spacing. However, this combination, although improving the DW image quality, is not sufficient for renal applications when higher resolution is required as, for example, to differentiate cortex and medulla. The readout segmentation of long variable echo train (RESOLVE) strategy has been proposed to improve the quality of DWI. With this technique, Porter and Heidemann showed a reduction of the signal blurring due to the $T_2^*$ decay during the echo-train in the phase-encoding direction. In this encoding scheme, k-space is divided into several shots along the readout direction in order to shorten the echo train length, leading to a longer acquisition time (approximately multiplied by the number of shots) compared to traditional ss-EPI DWI. Recently, improvements in renal interstitial fibrosis assessment was obtained by the use of the RESOLVE sequence associated with the cortico-medullary ADC difference ($\Delta$ADC) parameter. $\Delta$ADC derived from the RESOLVE sequence was used as a marker to detect a level of more than 40% interstitial fibrosis. In a homogenous population of kidney allograft patients undergoing biopsy, those with more than 40% interstitial fibrosis harbored a negative $\Delta$ADC, while a positive $\Delta$ADC was measured in patients with less than 40% interstitial fibrosis. Therefore, RESOLVE-derived $\Delta$ADC has a strong potential for clinical applications. However, the RESOLVE sequence is significantly longer than ss-EPI, which could be particularly disadvantageous in the abdomen, where respiratory triggering is mandatory. It is not known if the observed good correlation between $\Delta$ADC and interstitial fibrosis would still be valid with an MR sequence of shorter acquisition time, ie, ss-EPI. Therefore, the aim of the present study was to compare RESOLVE and ss-EPI DW sequences for the assessment of renal interstitial fibrosis.

Materials and Methods

Phantom

A home-made DWI phantom inspired by Lavdas et al was built to assess ADC quantification of ss-EPI and RESOLVE in a stable and reproducible manner. A plastic container of $14 \times 10 \times 9$ cm³ containing three plastic tubes was filled with nickel-doped agarose/sucrose gel. One tube was surrounded by a safflower oil-filled gap, and the second tube by an air-filled gap. The gel in the plastic container and tubes had two distinct ADC values (referred to as “1” and “2” as shown in Fig. 1).

Subjects

This study was performed according to the Declaration of Helsinki and the local Institutional Ethical Committee. Written informed consent for the MRI procedures was obtained from each subject. Eight healthy volunteers (three females and five males, with a mean age of 26 ± 2 years [23–29 years]), without known kidney disease or urinary system disease, and with an upper age limit of 30 years to avoid age-fibrosis related, were recruited.

A cohort of 27 CKD patients (2 native kidney, 25 kidney allografts) planned for a clinically driven kidney biopsy (9 females...
and 18 males, with a mean age of 53 ± 10 years [31–83 years]) was scanned with the same protocol as healthy volunteers. All CKD patients underwent, on the same afternoon, a research MRI examination, including a RESOLVE and ss-EPI DW sequences, in addition to the renal biopsy. Those acquiring and analyzing the MRI examinations were blinded for medical history and renal pathology assessment. As a subset analysis, the ADC from RESOLVE and the percentage of fibrosis from the first 25 kidney allograft recipients has already been published.\textsuperscript{12} Interstitial fibrosis was quantified histologically by a clinical pathologist (25 years of experience) and graded as a percentage from Masson trichrome staining. The percentage of cortical interstitial fibrosis derived from this examination of the kidney biopsy was considered the reference standard.

**MRI**

MRI was carried out on a 3T clinical Siemens Magnetom Trio (Tim system) scanner (Siemens, Erlangen, Germany) with a combination of the six elements phased-array abdominal coil and the integrated spine coil. The same protocol and coils were used for both phantom and subjects. For morphological images, 10 pseudo-cortical slices with the same spatial resolution and orientation as for DWI were acquired with both a T<sub>R</sub>-weighted Half Fourier acquisition single shot turbo spin echo (HASTE) and Look-Locker inversion recovery (MOLLI) T<sub>T</sub> mapping sequence.\textsuperscript{14} For the functional DWI assessment, the protocol included a navigator-triggered echo planar imaging (EPI) based single-shot readout MR scan (ss-EPI) using PACE (prospective acquisition correction technique) and a RESOLVE\textsuperscript{10,11} diffusion-weighted SE-EPI (spin echo based EPI) acquisition synchronized to the patient respiration, using a respiratory belt wrapped around the abdomen. For both ss-EPI and RESOLVE, the sequence parameters were TE/TR = 68/2200 msec, parallel imaging (generalized autocalibrating partially parallel acquisitions, GRAPPA) factor = 3, a bipolar diffusion scheme with the diffusion-encoding gradients applied in three orthogonal directions and 10 b-values (0, 10, 20, 40, 60, 150, 300, 500, 700, and 900 s/mm<sup>2</sup>), Shim settings and spatial resolution were strictly identical for all MR sequences. The five shot RESOLVE acquisition reduced echo spacing to 0.32 msec from 0.69 msec (ss-EPI) and increased acquisition time to 9.47 min ± 4' as compared to the ss-EPI at 2.20 min ± 1'17" depending on respiration.

**Image Analysis and Data Fitting**

MR analysis was performed blinded to histologic results. Freehand regions of interests (ROIs) were manually placed for quantification of both the cortex and medulla as previously described.\textsuperscript{12} In brief, two to three cortical ROIs followed the outer contour of the kidney and three medullary ROIs were traced on the T<sub>T</sub> maps and copied on b<sub>0</sub> images, avoiding artifacts, lesions, and major vessels. Signal intensity values inside ROIs were exported as .csv files with the OsiriX “export ROI” tool plugin and analyzed with MatLab (R2012b, MathWorks, Natick, MA) for diffusion data fitting using a Levenberg-Marquardt algorithm. The apparent diffusion coefficient (ADC) was calculated using a nonlinear least square method for the monoexponential fitting according to the following formula:

\[
ADC = \frac{1}{b} \log \left( \frac{S_i}{S_0} \right)
\]

(1)

where \(S_i\) is the signal intensity measured on the \(i^{th}\) b-value image and \(S_0\) is the signal amplitude in the absence of diffusion weighting (\(b = 0\) s/mm<sup>2</sup>). To separate the molecular diffusion from the microcirculation of blood in the capillary network (perfusion), the biexponential model\textsuperscript{15} was performed using the segmented fitting method\textsuperscript{16} with the following formula:

\[
\frac{S_i(b)}{S_0} = (1-F_p)e^{-b \cdot D} + F_p e^{-b \cdot (D^* + D)}
\]

(2)

where \(D\) is the diffusion coefficient representing “pure” molecular diffusion (slow component), \(D^*\) is the perfusion-induced pseudo-diffusion coefficient (fast component), and \(F_p\) is the perfusion fraction, ie, the fraction of the signal intensity \(S_0\) attributed to capillary blood flowing in each voxel (%). Considering that \(D^* \gg D\), the influence of \(D^*\) on signal decay was neglected for \(b > 200\) s/mm<sup>2</sup>. Therefore, \(D\) was first determined from monoexponential data fitting of the four highest b-values (\(b = 300, 500, 700, 900\) s/mm<sup>2</sup>) according to the following equation:

\[
S_i(b) = S_{int} \cdot e^{-b \cdot D}
\]

(3)

where \(S_{int}\) is the \(b_0\) intercept of the monoexponential fit of high b-value data. Then, \(F_p\) was calculated as:

\[
F_p = \frac{S_0 - S_{int}}{S_0}
\]

(4)

These values of \(D\) and \(F_p\) were then fixed, and \(D^*\) was calculated using a partially constrained non-linear regression of all data sets according to Eq. [2].

In all subjects (healthy volunteers and CKD patients), the cortico-medullary difference of each DW parameter (\(\Delta ADC, \Delta D, \Delta D^*, \Delta F_p\)) was defined in order to minimize interindividual variations. DW parameters were expressed as mean value in the ROIs ± standard deviation.

**Data Analysis**

Phantom results allowed us to quantify the ADC variability between DW sequences in stable and reproducible conditions. ROIs were manually drawn within the two different compartments using OsiriX software (http://www.osirix-viewer.com/). ADC comparison between (i) ss-EPI and (j) RESOLVE sequences was done using the coefficient of variation \(CV\) [%] expressed as:

\[
CV(i,j) = \frac{\sigma_{ADC(i,j)}}{\mu_{ADC(i,j)}} \times 100
\]

(5)

Comparison between ss-EPI and RESOLVE sequences was done in healthy volunteers, with a paired t-test between mean ∆DW parameters. An experienced uroradiologist (20 years) was consulted to ensure the quality of images for diagnostic purposes.

A fibrosis threshold of 40% was selected, as reported previously,\textsuperscript{12} to separate all subjects (healthy volunteers and CKD

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\[ ADC = \frac{1}{b} \log \left( \frac{S_i}{S_0} \right) \] (1)

where \(S_i\) is the signal intensity measured on the \(i^{th}\) b-value image and \(S_0\) is the signal amplitude in the absence of diffusion weighting (\(b = 0\) s/mm<sup>2</sup>). To separate the molecular diffusion from the microcirculation of blood in the capillary network (perfusion), the biexponential model\textsuperscript{15} was performed using the segmented fitting method\textsuperscript{16} with the following formula:

\[ \frac{S_i(b)}{S_0} = (1-F_p)e^{-b \cdot D} + F_p e^{-b \cdot (D^* + D)} \] (2)

where \(D\) is the diffusion coefficient representing “pure” molecular diffusion (slow component), \(D^*\) is the perfusion-induced pseudo-diffusion coefficient (fast component), and \(F_p\) is the perfusion fraction, ie, the fraction of the signal intensity \(S_0\) attributed to capillary blood flowing in each voxel (%). Considering that \(D^* \gg D\), the influence of \(D^*\) on signal decay was neglected for \(b > 200\) s/mm<sup>2</sup>. Therefore, \(D\) was first determined from monoexponential data fitting of the four highest b-values (\(b = 300, 500, 700, 900\) s/mm<sup>2</sup>) according to the following equation:

\[ S_i(b) = S_{int} \cdot e^{-b \cdot D} \] (3)

where \(S_{int}\) is the \(b_0\) intercept of the monoexponential fit of high b-value data. Then, \(F_p\) was calculated as:

\[ F_p = \frac{S_0 - S_{int}}{S_0} \] (4)

These values of \(D\) and \(F_p\) were then fixed, and \(D^*\) was calculated using a partially constrained non-linear regression of all data sets according to Eq. [2].

In all subjects (healthy volunteers and CKD patients), the cortico-medullary difference of each DW parameter (\(\Delta ADC, \Delta D, \Delta D^*, \Delta F_p\)) was defined in order to minimize interindividual variations. DW parameters were expressed as mean value in the ROIs ± standard deviation.

**Data Analysis**

Phantom results allowed us to quantify the ADC variability between DW sequences in stable and reproducible conditions. ROIs were manually drawn within the two different compartments using OsiriX software (http://www.osirix-viewer.com/). ADC comparison between (i) ss-EPI and (j) RESOLVE sequences was done using the coefficient of variation \(CV\) [%] expressed as:

\[ CV(i,j) = \frac{\sigma_{ADC(i,j)}}{\mu_{ADC(i,j)}} \times 100 \] (5)

Comparison between ss-EPI and RESOLVE sequences was done in healthy volunteers, with a paired t-test between mean ∆DW parameters. An experienced uroradiologist (20 years) was consulted to ensure the quality of images for diagnostic purposes.

A fibrosis threshold of 40% was selected, as reported previously,\textsuperscript{12} to separate all subjects (healthy volunteers and CKD.
patients) into two groups according to the level of fibrosis: one group (low to moderate fibrosis group) with a level of interstitial fibrosis lower than 40% (n = 28) and the second group (high fibrosis group) with more than 40% (n = 7). Welch's two-sample t-test was computed between groups for DWI parameters of ss-EPI and RESOLVE sequences. The limit of 40% of interstitial fibrosis was also used to stratify the area under the curves (AUC) of the receiver operating characteristics (ROC). ROC curves, plotting the true positive versus the false positive prediction rates, were used to assess the discrimination power of ∆ADC of ss-EPI and RESOLVE sequences. ROC curves were considered “paired.” Comparison between them was based on AUCs and done with the DeLong method,[15] available in the package pROC[16] of R software (v. 0.98.1091). The linear relationship between DWI parameters of both MR sequences and interstitial fibrosis was tested using the Pearson product-moment correlation coefficient. Linear correlations with P < 0.05 were considered “moderate” at R² > 0.20 and strong at R² > 0.45. The significance of the difference between correlation coefficients was performed using the Fisher Z-transform. A P-value of less than 0.05 was considered to indicate a statistically significant difference.

**Results**

**Phantom**

Compared to images from the RESOLVE sequence, the ADC map from ss-EPI showed more susceptibility artifacts due to the air-filled compartment, as shown in Fig. 1. However, no differences were found between ss-EPI and RESOLVE sequences for quantification of ADC when measured in the center of the phantom free of artifacts. Mean ADC values of each compartment are shown in Table 1. A coefficient of variation (CV) less than 3% was measured between the two DW sequences.

**Healthy Volunteers**

A cortico-medullary contrast with a positive ∆ADC, as shown in Fig. 2A, was measured with both DW sequences. In healthy volunteers, ss-EPI and RESOLVE sequences had no significant difference between DW parameters, as shown in Table 2.

**Interstitial Fibrosis Assessment**

The level of interstitial fibrosis measured in CKD patients from Masson trichrome ranged from 0–80% with a mean interstitial fibrosis of 31 ± 20%. 

### Table 1. ADC Values Measured in the Phantom for DWI with ss-EPI and RESOLVE Sequences

<table>
<thead>
<tr>
<th>Compartment</th>
<th>RESOLVE Mean ADC Values (σ) [10⁻⁶mm²/s]</th>
<th>ss-EPI Mean ADC Values (σ) [10⁻⁶mm²/s]</th>
</tr>
</thead>
<tbody>
<tr>
<td>“1”</td>
<td>1287 (45)</td>
<td>1359 (97)</td>
</tr>
<tr>
<td>“2”</td>
<td>1890 (34)</td>
<td>1903 (25)</td>
</tr>
</tbody>
</table>

For both DW sequences, ∆ADC was significantly lower in the high fibrosis group compared to the low fibrosis group (P = 0.003 for ss-EPI and P = 3.1 × 10⁻⁶ for RESOLVE). The RESOLVE sequence with ∆ADC led to a specificity and sensitivity of 100% and 86%, and the ss-EPI led to a specificity of 82% and sensitivity of 86% but, no significant difference of AUCs was measured between ss-EPI and RESOLVE using the fibrosis threshold of 40%, as shown in Fig. 3 (P = 0.16 between AUCs of ss-EPI and RESOLVE with Delong method).

∆ADC from both DW sequences was linearly correlated with the percentage of fibrosis, as shown in Fig. 4A. ∆ADC from RESOLVE had a significantly better correlation with interstitial fibrosis than AADC obtained with ss-EPI (P = 0.04, according to R² correlation comparison using the Fisher Z-transform).

Regarding the biexponential fitting parameters, a significant decrease of mean ∆D was measured in the high fibrosis group compared to the low fibrosis group for both sequences (P = 0.02 for ss-EPI and P = 8.2 × 10⁻⁵ for RESOLVE). However, for the remaining parameters (D* and Fp), no statistical difference was found between low and high fibrosis groups for either sequence. Regarding the correlation with interstitial fibrosis, only ∆D measured with the RESOLVE sequence was linearly related with renal interstitial fibrosis, as shown in Fig. 4B (R² = 0.29, P = 0.2 × 10⁻⁴). No statistical correlation was found with any of the DW parameters derived from the ss-EPI sequence and interstitial fibrosis (AD: R² = 0.12, AD*: R² = 0.08, ΔFp: R² = 0.01).

**Discussion**

The main result of this study is that the RESOLVE sequence derived ∆ADC (ADC cortico-medullary difference) was superior to ss-EPI-derived ∆ADC, as shown by a stronger linear correlation with the percentage of fibrosis from biopsy.

In the present study, we extended previous comparison of RESOLVE and ss-EPI sequences that were based only on image quality analysis[10] by including a comparison of DW parameters in a phantom and CKD patients. In the center of the gel phantom in a region free of susceptibility artifacts, no ADC difference was measured between ss-EPI and RESOLVE sequences, attesting the absence of systematic bias between both sequences.
However, the in vivo comparison demonstrated a clear advantage of the RESOLVE sequence over the ss-EPI sequence.

Several studies had previously found an improvement of the global DW image quality with the RESOLVE strategy due mainly to reduced $T_2^*$ blurring and susceptibility.
TABLE 2. Comparison of DW Parameters for ss-EPI and RESOLVE in 8 Healthy Volunteers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RESOLVE mean values (σ)</th>
<th>ss-EPI mean values (σ)</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC cortex $[10^{-6}\text{mm}^2/\text{s}]$</td>
<td>2250 (155)</td>
<td>2229 (173)</td>
<td>0.83</td>
</tr>
<tr>
<td>ADC medulla $[10^{-6}\text{mm}^2/\text{s}]$</td>
<td>1983 (161)</td>
<td>2046 (166)</td>
<td>0.47</td>
</tr>
<tr>
<td>ΔADC $[10^{-6}\text{mm}^2/\text{s}]$</td>
<td>267 (86)</td>
<td>183 (100)</td>
<td>0.28</td>
</tr>
<tr>
<td>D cortex $[10^{-6}\text{mm}^2/\text{s}]$</td>
<td>1788 (117)</td>
<td>1955 (162)</td>
<td>0.12</td>
</tr>
<tr>
<td>D medulla $[10^{-6}\text{mm}^2/\text{s}]$</td>
<td>1634 (88)</td>
<td>1849 (189)</td>
<td>0.08</td>
</tr>
<tr>
<td>ΔD $[10^{-6}\text{mm}^2/\text{s}]$</td>
<td>154 (109)</td>
<td>106 (58)</td>
<td>0.4</td>
</tr>
<tr>
<td>D* cortex $[10^{-6}\text{mm}^2/\text{s}]$</td>
<td>35704 (12563)</td>
<td>37621 (18159)</td>
<td>0.9</td>
</tr>
<tr>
<td>D* medulla $[10^{-6}\text{mm}^2/\text{s}]$</td>
<td>31508 (12787)</td>
<td>41613 (26793)</td>
<td>0.46</td>
</tr>
<tr>
<td>ΔD* $[10^{-6}\text{mm}^2/\text{s}]$</td>
<td>4196 (24561)</td>
<td>3992 (21680)</td>
<td>0.68</td>
</tr>
<tr>
<td>Fp cortex [%]</td>
<td>23 (8)</td>
<td>16 (8)</td>
<td>0.19</td>
</tr>
<tr>
<td>Fp medulla [%]</td>
<td>18 (8)</td>
<td>16 (8)</td>
<td>0.66</td>
</tr>
<tr>
<td>Δ Fp [%]</td>
<td>5 (8)</td>
<td>0.25 (9)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

No significant difference in all DW parameters was seen between ss-EPI and RESOLVE sequences. $P > 0.05$ for all parameters/markers.
effects, mainly resulting in an enhancement of tumor lesion detection in various organs, such as head and neck region, breast, pelvis, thyroid, and rectum. All these studies showed that the greater tumor lesion to normal tissue contrast from RESOLVE resulted in a better ADC differentiation of healthy tissues and tumors. Except in one study of the parotid glands, which showed no significant difference in tumoral ADC values between RESOLVE and ss-EPI, a significantly lower ADC value was always measured with the readout-segmented strategy within malignant lesions in all these other studies. In our study, a larger negative ΔADC was measured with RESOLVE by comparison to ss-EPI in patients with more than 40% of interstitial fibrosis. The explanation of this ADC difference between RESOLVE and ss-EPI measured in pathologies, but not seen in healthy tissues, is still unclear and under debate. The better delineation of lesions by the RESOLVE sequence could decrease the averaging with adjacent high ADC values of normal tissues and, thus, preserve the lower ADC values in the tumor as observed in breast cancer. However, Zhao et al contested that adjacent

FIGURE 3: AUC of the ROC using 40% of interstitial fibrosis as a limit for renal fibrosis detection by ΔADC. All patients with more than 40% of interstitial fibrosis had a negative ΔADC, whereas all patients with less than 40% had a positive ΔADC, resulting in a larger AUC from the RESOLVE sequence obtained with 10 b-values equal to 1. A weaker ability to separate a high level and low level of fibrosis was measured with the ss-EPI sequence with a reduced AUC, attesting the presence of true positive and/or false positive. However, no significant difference of AUCs was measured between ss-EPI and RESOLVE using the fibrosis threshold of 40%.

FIGURE 4: Correlations between ΔADC (A), ΔD (B), ΔD* (C), ΔFp (D) and renal interstitial fibrosis from ss-EPI and RESOLVE sequences. Data were acquired from 35 subjects (27 CKD patients and eight healthy volunteers). ΔADC from RESOLVE was better correlated to renal interstitial fibrosis than ΔADC from ss-EPI (P = 0.04 by R² correlation comparison using the Fisher Z-transform). Regarding biexponential fitting parameters, correlations between ΔD and renal interstitial fibrosis were observed for the RESOLVE sequence only. ΔADC from ss-EPI and ΔD from RESOLVE gave equivalent correlation with the percentage of fibrosis. All other correlations were not significant, suggesting that the intravoxel incoherent motion parameters of perfusion (ΔD*) and fraction of perfusion (ΔFp) were not linked to renal interstitial fibrosis in our population.
high ADC values of normal tissues could impact the ADC values measured in the lesion. They compared in terms of ADC values, RESOLVE, and ss-EPI in the brainstem and sinonasal lesions. The sinonasal lesions, which were not surrounded by high ADC values of normal tissues, had significantly lower ADC values on RESOLVE compared to ss-EPI. By contrast, the brainstem measurements, less affected by the susceptibility artifacts and ghosts than sinonasal lesions, exhibited no significant differences between the two DW sequences. They concluded that the difference in ADC values could be more attributed to susceptibility artifacts and ghosts, present in the sinonasal lesions DW images, than by adjacent high ADC values of normal tissues. In our case, both effects (ie, a reduction of susceptibility effects preserving the cortex from artifacts and an improved anatomical delineation) could explain the better performance of the RESOLVE sequence.

The biexponential-fitting values measured in the current study had comparable values with those reported in previous studies on kidney allograft patients, but did not allow us to discriminate the level of interstitial fibrosis. The biexponential-fitting parameters with either the ss-EPI or RESOLVE sequence were not significantly correlated with the percentage of fibrosis from biopsy. We therefore concluded that the biexponential model is inadequate to robustly assess the percentage of kidney fibrosis in our population. This result was consistent with another study, which found an absence of correlation in diffuse liver fibrosis. In addition, biexponential parameters in the kidney have been shown not to correlate significantly with enhanced glomerular filtration rate (eGFR), which is in turn correlated with renal interstitial fibrosis. The major difficulties of using a biexponential fitting are the large variability in the resulting parameters and the lack of robustness against noise. Also, despite the use of physiological triggering schemes to limit respiratory artifacts, physiological motion artifacts that lead to inhomogeneous signal dropout can impact kidney images. We might expect that biexponential fitting would be more sensitive to decreases of signal intensity, as more points are needed to build the fit.

An increase of \(D^*\) has been measured with the increase of eGFR. However, the correlation was relatively weak, probably due to the large variability of \(D^*\) due to the fitting. An interpatient coefficient of variation (CV) of 25% was found for the \(F_p\) parameter in a study on the variability of biexponential parameters in renal allograft patient after transplantation (5–19 days). Despite the use of the cortico-medullary difference and the RESOLVE sequence, which reduced intersubject variability compared to the cortical or medullary ADC, we found that biexponential parameters with \(\Delta D\), \(\Delta D^*\), and \(\Delta F_p\) did not accurately assess renal fibrosis. The relevance of the biexponential model in general is still subject to debate.

There are some inherent limitations of our study. The size of our population was restricted, especially in terms of patients with a high level of fibrosis (>40%), as few patients with acute kidney disease or CKD and a high level of fibrosis had routine biopsy. Fibrosis in healthy volunteers was not measured, but these subjects were considered to have no fibrosis. This could introduce an additional error; however, such an assumption is valid in a relatively young population, all under 30 years of age, thus avoiding age-related fibrosis. The lack of perfusion in the diffusion phantom limits its use to ADC calculation in stable and reproducible condition and does not allow biexponential fitting parameters assessment. An implementation of Lemke’s correction by acquiring \(T_1\) and \(T_2\) maps would be appropriate to take into account \(T_2\) effects and correct the \(F_p\) parameter for the biexponential. However, in case of chronic disease, we would not expect a significant difference in \(T_2\) values between subjects, and therefore the uncorrected \(F_p\), while not the true value, could be compared between the DW sequences.

Finally, this study supports the advantages of \(\Delta \text{ADC}\) from the RESOLVE sequence to assess renal interstitial fibrosis, despite the longer acquisition time compared to the conventional ss-EPI. An alternative approach would be to acquire the ss-EPI sequence with more averages on b-values such that the scan time would have been equivalent to RESOLVE. This strategy could be used to increase the signal-to-noise ratio and therefore improve ss-EPI analysis. However, this would not correct for off-resonance effects maintaining this disadvantage over RESOLVE. The initial goal of this study was to verify if there is a benefit of using the RESOLVE strategy compared to the inherently shorter acquisition time ss-EPI. It would be worthwhile in future work to verify if reducing the number of b-values could shorten the acquisition time without impacting DW parameters. Such an analysis is beyond the scope of the current study aiming to compare ss-EPI and RESOLVE with DW parameters obtained with monoexponential and biexponential fitting for interstitial fibrosis assessment.

In conclusion, \(\Delta \text{ADC}\) derived from both RESOLVE and ss-EPI is sensitive to fibrosis. \(\Delta \text{ADC}\) from RESOLVE has a significantly better correlation with interstitial fibrosis than \(\Delta \text{ADC}\) from ss-EPI. Biexponential-fitting parameters showed no advantage for renal interstitial fibrosis assessment for either sequence. Despite a longer acquisition time compared to ss-EPI, the use of the RESOLVE sequence with \(\Delta \text{ADC}\) calculation to assess renal interstitial fibrosis is therefore recommended.

Acknowledgments

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References


2.3.1 Supplementary Publication 3

Impact of the reduction of the number of b-values (10 b-values versus 5 b-values)

The primary motivation of this complementary study was to compare diagnostic performance of 10 b-value versus 5 b-value DWI in the detection of interstitial fibrosis with ss-EPI and RESOLVE sequences. Using the data from the third publication [27] (same phantom and population, as well as same materials and methods), the cortico-medullary difference (ΔADC) calculated with 5 b-values (0, 10, 40, 300, 700 s/mm²) was extracted from the 10 b-value acquisition and compared with the full set of 10 b-values (0, 10, 20, 40, 60, 150, 300, 500, 700 and 900 s/mm²).

In a phantom, a coefficient of variation (CV) of ADC less than 3% was measured between the DW sequences, for both 10 and 5 b-values. In healthy volunteers, ΔADCs from 5 b-values (ss-EPI and RESOLVE) were equivalent, without significant difference between both sequences (p=0.41 according to the paired t test). A significant increase of ΔADC from 10 b-values compared to those from 5 b-values was however measured for the RESOLVE sequence (p<0.05), but not for the ss-EPI sequence (p = 0.14). As in the previous publication, all subjects (healthy volunteers and CKD patients) were divided into two groups according to the level of interstitial fibrosis (low fibrosis group if the percentage of interstitial fibrosis was less than 40% and high fibrosis group if strictly more than 40%). For both DW sequences, ΔADC (5 and 10 b-values) was significantly lower in the high fibrosis group compared to the low fibrosis group (p<0.05 for ss-EPI and p<0.001 for RESOLVE). No significant difference for area under the curves (AUCs) of the receiver operating characteristics (ROC) was measured between ss-EPI and RESOLVE using the fibrosis threshold of 40% from either 5 or 10 b-values (Figure 18) with p=0.45 (between AUCs of ss-EPI and RESOLVE (5 b-values)) and p=0.16 (between AUCs of ss-EPI and RESOLVE (10 b-values)) with the Delong method. However, when reducing the number of b-values to 5, both ss-EPI and RESOLVE sequences lost significantly in classification performance (comparison of AUCs) with p=0.006 and p=0.001 respectively. A specificity of 86% and sensitivity of 71% was computed for RESOLVE, and a specificity of 89% and sensitivity of 57% for ss-EPI for 5 b-values.

ΔADC (5 and 10 b-values) from both DW sequences was linearly correlated to the percentage of fibrosis (Figure 19). ΔADC (5 b-values) from ss-EPI and RESOLVE was equivalent in performance to assess renal interstitial fibrosis (R² = 0.26, p<0.05 for ss-EPI and R² = 0.31, p<0.05 for RESOLVE). However, ΔADC from RESOLVE 10 b-values had a significantly better correlation with interstitial fibrosis than ΔADC obtained with RESOLVE 5 b-values (p=0.05) or ss-EPI (10 and 5 b-values) (p=0.04) according to R² correlation comparison using the Fisher Z-transform.

In conclusion, the previously observed strong correlation between RESOLVE with ΔADC (from 10 b-values) and the percentage of renal interstitial fibrosis could not be reached by reducing by half the number of b-values. With 5 b-values, RESOLVE significantly degrades in efficiency and both DW sequences became equivalent for fibrosis assessment. Two hypotheses could be envisaged to explain this observation. First, increasing the number of b-values could provide a greater robustness against noise and motion artifact that may affect individual signal intensity data. Also, the b-value sampling may be suboptimal for the fitting of signal intensity decay associated with renal fibrosis.
Figure 18: ROC curves for \( \Delta \text{ADC} \) using 40% as a threshold for fibrosis detection. 5 b-value and 10 b-value ss-EPI and RESOLVE sequences were compared. All patients with more than 40% fibrosis had a negative \( \Delta \text{ADC} \), with a positive \( \Delta \text{ADC} \) in cases of lower fibrosis, resulting in an AUC from the RESOLVE sequence obtained with 10 b-values equal to 1. A poorer ability to separate high level and low level of fibrosis was measured with the RESOLVE sequence (5 b-values) and with the ss-EPI sequence (5 and 10 b-values) with a reduced AUC attesting the presence of true positive prediction and/or false positive prediction.

Figure 19: Correlations between \( \Delta \text{ADC} \) and renal interstitial fibrosis (from 10b-values in the 1st graph and 5 b-values in the 2nd graph) from ss-EPI and RESOLVE sequences were obtained in 35 subjects (27 CKD patients and 8 healthy volunteers). \( \Delta \text{ADC} \) from 10 b-values RESOLVE was better correlated to fibrosis than \( \Delta \text{ADC} \) from 5 b-values of the RESOLVE sequence (\( p=0.05 \) by R² correlation comparison using the Fisher Z-transform), and than \( \Delta \text{ADC} \) obtained with the ss-EPI sequence (10 b-values or 5 b-values) with \( p=0.04 \) by R² correlation comparison using the Fisher Z-transform.
2.4 Publication 4

Reproducibility of $\Delta$ADC on different MR systems

Manuscript in preparation for publication

In the present study, the reproducibility of kidney ADC values was assessed in a DWI phantom and in healthy volunteers on 5 different MR systems (1.5T and 3T, Siemens and Philips).

Despite the optimized protocol including RESOLVE, a large ADC variability persists between patients with the same percentage of fibrosis. More importantly, the ADC variability problems also occurred in healthy volunteers without known renal dysfunction. ADC variability in a sample of healthy volunteers could arise from different sources, and the exact cause of the ADC variability is still undetermined. The absence of recognized reference values for healthy kidney ADC prevents definition of an abnormal ADC threshold suitable for diagnosis and, consequently, limits the use of ADC in clinical practice. Part of the variability could be derived from differences in system hardware (gradients strength and slew rate), and in differences in acquisition protocols. In particular, ADC is influenced by the diffusion encoding strategy, b-values and echo time (TE). In addition to technical sources of ADC bias, physiological factors can influence ADC values. Physiological differences such as hydration level, the proximity of air in the intestine, as well as physiological motion such as respiratory motion or variations in blood flow in the organ of interest during the cardiac cycle, can lead to artifacts and uncertainty in DWI quantification in the kidney.

The phantom allowed assessment of hardware and sequence based sources of ADC bias under stable conditions, without physiological sources of variation such as motion or hydration level. Healthy volunteers were then scanned on the same machines sequentially, and in random order, to assess reproducibility of kidney ADC. In healthy volunteers, significant inter-vendor differences, as well as significant difference between 1.5T and 3T (Siemens), for ADC in the cortex and medulla were measured with the Wilcoxon test. The cortico-medullary difference $\Delta$ADC allowed reduction of ADC variations between MR systems such that they were no longer significantly different. This ADC variability could not be explained purely by the differences between parameters and hardware since the variation of ADC values between MR systems from different vendors and field strength was below 10% in the phantom. Importantly, the $\Delta$ADC parameter allowed reduction of ADC variation between systems and $\Delta$ADC was a more robust parameter than cortical or medullary ADC alone.
The Cortico-Medullary ADC Difference Reduces Inter-System Variability in Renal Diffusion-Weighted Imaging

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Running title: Reduction of Inter-System Variability in Renal DWI
Introduction:
Renal apparent diffusion coefficient (ADC) measurements from diffusion-weighted imaging (DWI) have been suggested as a diagnostic tool for kidney pathologies (1-4). However, the comparison of renal ADC values from different studies is still difficult despite attempts for a standardized protocol (5,6). Direct comparison of ADC values from different MR systems or field strengths is currently considered unreliable, even at equivalent b-values in the DWI acquisition (7-9). A meta-analysis of 19 studies reported a large range of ADC values in healthy renal parenchyma from $2000 \times 10^{-6}$ to $4100 \times 10^{-6}$ mm$^2$/s for the renal cortex and $1900 \times 10^{-6}$ to $5100 \times 10^{-6}$ mm$^2$/s for the medulla (10). The absence of recognized reference values for healthy kidney ADC prevents definition of abnormal ADC threshold suitable for diagnosis, and consequently, limits the use of ADC in clinical practice. The exact causes of the large inter-study ADC variability are still undetermined. Part of the variability could be derived from differences in system hardware (gradients strength and slew rate) (11), and in differences in acquisition protocols. In particular, ADC is influenced by the diffusion encoding strategy (8,12), b-values (13,14) and echo time (TE) (15). In addition to technical sources of ADC bias, physiological factors can influence ADC values. Physiological differences such as hydration level (16), the proximity of air in the intestine (17), as well as physiological motion such as respiratory motion (18) or variations in blood flow in the organ of interest during the cardiac cycle (19), can lead to artifacts and uncertainty in DWI quantification in the kidney.
As recently shown, the cortico-medullary difference, ΔADC, is strongly correlated to renal interstitial fibrosis (20). ΔADC reduced inter-subject variability in comparison to separate cortical or medullary ADC. ΔADC could be a valuable index to compare kidney ADC across MR systems in case of kidney diseases affecting primarily the cortex, such as acute or chronic renal failure, renal artery stenosis, and interstitial fibrosis. The medulla, used as an internal reference, is an ideal candidate for normalization because of its close proximity to the cortical tissue. Subtraction of the medullary ADC, instead of normalization using surrounding tissues outside the kidney, decreased possible errors related to non-linearity of gradients, B₁ and B₀ heterogeneity or, related to the coil sensitivity profile (21-23). In chronic kidney disease patients, ΔADC was more correlated than cortical ADC with interstitial fibrosis and was therefore considered as potential biomarkers for kidney fibrosis evaluation (20). The author found that ΔADC decreased variability between patients of the same level of fibrosis compared to absolute cortical ADC values. An important remaining question is if the variability of ADC between MR systems can be reduced by ΔADC.

The purpose of this study was to determine the reproducibility of kidney ADC values in a DWI phantom and in healthy volunteers on 5 different MR systems (1.5T and 3T, Siemens and Philips). The phantom allowed assessment of hardware and sequence based sources of ADC bias under stable conditions, without physiological sources of variation such as motion or hydration level. Healthy volunteers were, then, scanned on the same machines sequentially, and in random order, to assess reproducibility of kidney
ADC. The goal was to verify that the cortico-medullary difference $\Delta$ADC was a more robust parameter, with a reduced variability, than cortical or medullary ADC.

**Materials and Methods:**

*Phantom:* A plastic container phantom, the same as in a previous study looking at the comparison of ADC values of readout-segmented echo-planar imaging (EPI) and single-shot (EPI) DWI (24), was used to assess ADC reproducibility in a stable and reproducible manner, across the different MR systems without any physiological variation. The phantom contained three plastic tubes filled with nickel-doped agarose/sucrose gel. One tube was surrounded by a safflower oil-filled gap; the second tube by an air-filled gap and the third one was directly in contact with the gel in the plastic container. Two different concentrations of nickel-doped agarose/sucrose resulted in different ADC values of the gel in the plastic container and tubes.

*Healthy Volunteers:* This study was performed according to guidelines of the Declaration of Helsinki and the local institutional ethical committee. Eight healthy volunteers comprising 4 females and 4 males, with a mean age of 35 ± 9 years (median 32 years, range 24-58 years), were recruited after informed consent. Volunteers enrolled in this study had no known kidney disease or urinary system disease. Scanning on all MR systems was done in the same session to minimize physiological variation, but with no specific instructions for hydration state. In addition, the order of scanners was deliberately changed between volunteers.
**Acquisition Protocols:** Single-shot Echo-Planar (ss-EPI) DW images were acquired on Siemens MR systems (AERA 1.5T; PRISMA 3T; SKYRA 3T) and Philips MR systems (INGENIA 1.5T; Ingenuity TF PET/MR 3T composed of an Achieva 3T TX MRI, called ACHIEVA 3T in this study). The phantom and healthy volunteers were scanned with the same imaging parameters, in coronal-oblique slice orientation, with the phased array abdominal and the spine coils. The diffusion-encoding gradients were applied in 3 orthogonal directions with 3 b-values (0, 500, 700 s/mm$^2$) and a bipolar diffusion gradient scheme. Complete DWI protocol parameters are summarized in table 1.

<table>
<thead>
<tr>
<th></th>
<th>SKYRA 3T</th>
<th>PRISMA 3T</th>
<th>AERA 1.5T</th>
<th>ACHIEVA 3T</th>
<th>INGENIA 1.5T</th>
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<td>Spectral selectivity suppression</td>
<td>Spectral selectivity suppression</td>
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<td>43</td>
<td>63</td>
<td>41</td>
<td>103</td>
<td>95</td>
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**Table 1:** Specifications of the MR systems and DWI parameters

All DWI acquisitions were performed in breathhold for the volunteers with acquisition times between 18 and 26 seconds. $T_2$-weighted half-Fourier single-shot turbo spin echo
(HASTE) images were also acquired as reference anatomical image quality with the same resolution and slice orientation as the DW protocol.

**ADC quantification:** Apparent Diffusion Coefficient (ADC) [mm²/s] was measured on quantitative ADC maps generated automatically by the OsiriX ADCmap plugin (OsiriX Open source http://www.osirix-viewer.com) from a monoexponential fit of the three b-values. In the phantom, two circular regions of interest (ROIs) were placed directly on the ADC map, one in the gel within the main plastic container (Compartment ‘C1’) and, the second in the gel at the center of the tube surrounded by oil (Compartment ‘C2’). The difference C1-C2 was calculated. In healthy volunteers, the b₀ image was used as a reference anatomical image for ROIs along with comparison to the HASTE images. ROIs were placed, as previously described (20), for separate analysis of the cortex and medulla. The cortico-medullary difference ΔADC was defined as

\[ \Delta \text{ADC} = <\text{ADC}_{\text{cortex}} > - <\text{ADC}_{\text{medulla}} > \]

**Statistical analysis:** In the phantom, ADC values, presented as mean ± standard deviation of all voxels in the ROIs of compartment ‘C1’ and compartment ‘C2’ separately. Inter-scan agreement of ADC measurements between MR systems was assessed via coefficient of variation (CV, %). CV was calculated as the standard deviation of the inter-scan ADC values, divided by the mean ADC values of each pair combination of MR scanners. By measuring the CV in the phantom, the variation purely due to MR systems from the same field strength, between 1.5T and 3T and between Siemens and Philips vendors was assessed in a homogenous media.
In healthy volunteers, statistical analysis of mean ADC values (cortex, medulla and Δ) from the different MR systems was carried out in several steps. In a preliminary observation, normal distribution of ADC values was assessed by Shapiro-Wilk test and visually, using histograms of data distribution. It was decided to use non-parametric statistical tests due to the relative small sample size and as non-normal distribution could not be rejected. First, inter-scan agreement of ADC measurements was assessed, as in the phantom, via coefficient of variation to contrast ADC measurements in the two separate tissues of the renal parenchyma (cortex and medulla) to the ADC variability measured with the phantom. All ADC measurements (cortex, medulla and Δ) were displayed in a boxplot, and significant differences of median ADC values measured over all healthy volunteers, between vendors and between field strengths, were estimated using the Wilcoxon signed rank test. For the Wilcoxon signed rank test, a p-value of less than 0.05 was considered to indicate statistical significance. Furthermore, the Spearman correlation was used to assess if there is an association between ADC of the different MR systems that can be described using a monotonic function. The Spearman correlation tested for a statistical dependence as a systematic bias between ADC values measured across all MR systems. For each set of correlations, the required level of statistical significance was subject to a Bonferroni correction to control for type one error \( p < \frac{0.05}{10} = 0.005 \) with 10 the number of correlations tested). Statistical analyses were performed using the stats R package version 3.1.1.
**Results:**

**Phantom:** Figure 1 shows examples of ADC maps of the phantom for all MR systems. Despite deformations, particularly visible on ACHIEVA 3T system, all DW images were suitable for ADC analysis as the mean ADC values of each compartment were measured in the center of the phantom and therefore free of artifacts.

![ADC Maps of Phantom](image)

*Figure 1: The phantom contained two tubes. One tube was surrounded by a safflower oil-filled gap, and the second tube by an air-filled gap.*

These data are summarized in Figure 2. All coefficients of variation (CVs) between MR systems and field strengths were below 10%. Overall, across the five MR scanners, the CVs measured in compartment C1, C2 and the difference C1-C2, were 4.8%±2.9%, 5.0%±3.6% and 4.2%±2.5%, respectively.
Figure 2: The bar chart shows the ADC values measured for compartment C1 and C2, as well as the difference between C1 and C2, across all 5 MR systems.

Healthy volunteers: DWI acquisition on all 5 systems was completed in 7 healthy volunteers. For the eighth volunteers, there was no data for the INGENIA scanner due to poor subject compliance. DW image quality was suitable for ADC analysis in all cases, as shown with the example ADC maps in Figure 3.
Figure 3. Example of coronal-oblique ADC maps of a right kidney. Arrows point to the cortex and medulla. In healthy volunteer, the cortico-medullary difference is clearly well delineated.

The ADC values [×10⁻⁶ mm²/s] had a range from 2048 to 2173 for the cortex, 1785 to 1958 for the medulla, and 206 to 263 for the ΔADC as shown in detail in table 2.

<table>
<thead>
<tr>
<th>ADC (sdev) [mm²/s]</th>
<th>SKYRA 3T</th>
<th>PRISMA 3T</th>
<th>AERA 1.5T</th>
<th>ACHIEVA 3T</th>
<th>INGENIA 1.5T</th>
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<tr>
<td>Cortex</td>
<td>2106 (139)</td>
<td>2121 (183)</td>
<td>2048 (169)</td>
<td>2098 (236)</td>
<td>2173 (308)</td>
</tr>
<tr>
<td>Medulla</td>
<td>1880 (215)</td>
<td>1915 (207)</td>
<td>1785 (35)</td>
<td>1868 (272)</td>
<td>1958 (193)</td>
</tr>
<tr>
<td>Δ</td>
<td>226 (59)</td>
<td>206 (80)</td>
<td>263 (88)</td>
<td>230 (81)</td>
<td>215 (78)</td>
</tr>
</tbody>
</table>

Table 2: Mean ADC values measured in healthy volunteers
Figure 4 shows a boxplot with mean ADC measured in the 8 healthy subjects.

Figure 4. Boxplot illustrating the mean ADC values \([10^{-6}\text{ mm}^2/\text{s}]\) for all MR systems for the cortex, medulla and Δ. Data were obtained in 8 healthy volunteers. Significance was defined as p-value of less than 0.05 (*). A highly significant difference is indicated between the cortex and medulla of PRISMA 3T and AERA 1.5T, as well as between AERA 1.5T and INGENIA 1.5T. No significant differences were measured between the ΔADC parameters.
The Wilcoxon test showed no significant difference between the three 3T MR scanners for the cortical ADC (p-values ranging from 0.74 to 0.84), medullary ADC (p-values from 0.54 to 0.64) and ΔADC (p-values from 0.15 to 0.94). However, significant differences in renal and medullary ADC were measured between Siemens MR scanners at 1.5 and 3T (p=0.016 for cortex and p=0.008 for medulla of PRISMA 3T and AERA 1.5T) and between scanners from different vendors at 1.5T (p=0.047 for cortical ADC of AERA and INGENIA). No such significant difference was measured using the ΔADC parameter across all MR systems with all p>0.05 (range 0.15-0.94). Coefficients of variation (CVs) measured in healthy volunteers were superior to those measured in the phantom as shown in Figure 5.
The mean CV of a volunteer across all MR systems was 7%±2% for the cortex and 9%±3% for the medulla. The mean CV (averaging cortex and medulla) was 10% ± 4% between MR systems of 1.5T (AERA and INGENIA) and 7% ± 6% between MR systems of 3T (SKYRA, PRISMA and ACHIEVA). A comparable CV was measured when comparing 1.5T and 3T MR systems, or when comparing Philips and Siemens MR systems with, in both cases, 7% ± 5% variability (maximum value 24% comparing 3T to 1.5T and 25% comparing Siemens to Philips). Overall, the highest coefficient of variation was obtained between medullary ADC measured at 1.5T with a CV of 10% ± 4% (up to 25%).

No significant relationship was measured by comparing cortical ADC, medullary ADC and ΔADC values across all MR systems with the Spearman correlation (all p-values > 0.005 for all 10 pairs of correlations considered). This lack of correlation indicates that ADC values measured on one MR system were not directly related to those measured on another by a simple monotonic function. Consequently, a simple monotonic function or a systematic bias of ADC values could not be applied to compare ADC values of different MR scanners.
Discussion:

The main result of this study is that, in healthy volunteers, significant inter-vendor differences, as well as significant difference between 1.5T and 3T (Siemens), for ADC in the cortex and medulla were measured with the Wilcoxon test. ΔADC allowed reduction of ADC variations between MR systems. This ADC variability could not be explained purely by the differences between parameters and hardware since the variation of ADC values between MR systems from different vendors and field strength was below 10% in the center of the phantom, free for artifact. Only few studies used phantoms for multi-scanner DWI comparison, with generally two types of phantom. Water and ice water phantoms (a central tube filled with distilled water surrounded by ice) were previously used to be highly reproducible and eliminate temperature variation (5,25-27). Keenan et al (22) built a breast tissue-equivalent diffusivity phantom based on polyvinylpyrrolidone to represent ADC values for malignant masses and benign lesions. In theses previous studies, the majority of mean ADC measurements (80% to 86%) were measured within 5% from the nominal value and all within 10%. ADC variability measured in the current study was in agreement with those studies with a mean of 4% coefficient of variation measured in the phantom. It is noteworthy that the phantom, first inspired by Lavdas et al. (28), was built to reproduce common pitfalls and artifacts induced by the presence of fat (with one compartment filled with oil) and air (with the air-filled gap). Despite, deformations due to susceptibility effects and differences in fat saturation techniques between the systems, the current coefficient of variation for ADC values in the phantom was considered as acceptable and could be used as a baseline of ADC variation.
In healthy volunteers, the mean coefficients of variation measured in this study match the CV range previously found in kidney ADC (11). Despite relatively small mean ADC variations between MR systems (around 7 to 10%), a large maximum ADC variation (up to 25%) induced significant differences between the MR systems. In contrast to a previous study using other Siemens, Philips and GE systems (11), which found significant ADC differences for the cortex and medulla between 3T MR systems of different vendors and no significant difference in mean cortical and medullary ADC values between 1.5T and 3T from the same vendors, we found a significant ADC difference between PRISMA 3T and AERA 1.5T, as well as between AERA 1.5T and INGENIA 1.5T. All significant differences of ADC inter-scanner, measured with the Wilcoxon test, were reduced in subjects through the use of the cortico-medullary difference, ΔADC index.

The wider range of the cortex and medulla ADC values compared to the phantom ADC values on a single machine may be attributed to different physiological status between volunteers, such as level of hydration, motion, respiration pattern, and peristaltism. A simple approach to reduce variability of DWI quantification could, therefore, be normalization (defined as ADC tissue or lesions / ADC reference site), as already reported in the ADC measured in the abdomen (9,29-32). Typically, in liver assessment, the spleen was used as reference for normalized liver ADC. Do et al (29) found a significant difference between healthy to intermediate stage fibrosis using normalized liver ADC, whereas absolute liver ADC could only distinguish cirrhosis from normal liver. In this previous study, the normalization improved the diagnostic accuracy for detection of liver fibrosis. However, the major limitation with the use of an external organ as reference is the
possible presence of undiagnosed pathology in that organ, which could add uncertainty to the normalization. In a study of pelvic lymph nodes, the renal cortex was used as a reference site for differentiating metastatic from non metastatic pelvic lymph nodes at 1.5T (33). In addition, cortical ADC could be altered in various diseases and, consequently, renal cortex could not be used for ADC normalization in patients with chronic kidney diseases because of the degradation of the renal cortex. To counteract physiological variation, normalization with the ADC of an external reference of a 20 ml saline bottle placed on the groin has been used in prostate cancer assessment. This strategy gave a significantly better area under the ROC curve compared to those of tumoral ADC without any normalization, or in comparison to normalization using the obturator internus muscle, or urine in the bladder (34). To use an external bottle as reference site for kidney DWI would require an increased field-of-view, thereby increasing artifacts due to increased EPI readout. Moreover, shim errors, as well as gradient nonlinearity bias, would increase ADC variability (21-23). Malyarenko et al. (23) showed that a major contribution to systematic ADC bias comes from gradient nonlinearity. ADC variability measurements were substantially influenced by the spatial location of the imaged organ. ADC non-uniformity increases with the distance from isocentre. Correction techniques for gradient nonlinearity bias are supplied by vendors but are complex to set up for the users. Crucially, the close proximity of the medulla and cortex in the current study decreased errors related to $B_1$ and $B_0$ heterogeneity, as well as gradient nonlinearity.

In this study, acquisition protocols, while comparable, could not be identical. For example, TE was not kept constant in each acquisition protocol, as it was set as the
minimum possible on each system. This could directly alter ADC values (15). However, as in clinical practice all systems are not equivalent, the \( \Delta \text{ADC} \) index could be used to compare studies of different MR systems.

In conclusion, Variability of ADC in the cortex and medulla observed between different MR systems is reduced by the use of the \( \Delta \text{ADC} \).

References:


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weighted magnetic resonance imaging at 1.5 Tesla in phantom and in soft tissues of the abdomen. Journal of computer assisted tomography 2013;37(1):46-51.


30. Papanikolaou N, Gourtsoyianni S, Yarmenitis S, Maris T, Gourtsoyiannis N. Comparison between two-point and four-point methods for quantification of apparent diffusion


2.5 Publication 5

Motion Compensation

Manuscript submitted in JMRI

The goal of this publication was to evaluate the impact of confounding motion on ADC, and to propose a method for motion compensation.

In the previous publication regarding the inter-system reproducibility of ADC, a wide range of cortical and medullary ADC values was measured in healthy volunteers on a single MR system. The variability of ADC between healthy volunteers could be attributed to different physiological status, as less than 5% of ADC variation was measured in the phantom. Kidney motion induced a major additional artifact (with susceptibility), which could be visualized as a shift between DW images of consecutive b-values, image blurring and/or signal loss in DW images (as explained in the second part of the introduction chapter). Shift or blur could be respectively corrected or excluded. Signal intensity dropout within DW images used to calculate the ADC is the most challenging case, leading to a poor fit of the diffusion data.

In this PhD work (supplementary material of the third publication [27]), the improvement of the correlation (ADC versus fibrosis) with RESOLVE acquired with the higher number of 10 b-values was attributed in part to a better robustness of the fit against inherent motion and noise that can affect the signal intensity of individual b-values. However, increasing the number of b-values also increased the acquisition time and did not completely minimize localized signal loss in DW images. In interstitial fibrosis assessment, where small diffuse heterogeneities are investigated, any motional signal intensity dropout needs to be overcome. Currently, one way to investigate the impact of signal dropout on ADC is to assess the variability between consecutive slices. This information is lacking in the literature. In the following publication, signal intensity and ADC inter-acquisition, inter-slice and inter-individual variability was first quantified in healthy volunteers. Then, a motion compensation method, based on Temporal Maximum Intensity Projections (TMIPs) was proposed to compensate the signal intensity dropout in renal DWI and reduce the ADC variability.
### Variability Reduction in Renal Diffusion-Weighted Magnetic Resonance Imaging with Motion Compensation

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Variability Reduction in Renal Diffusion-Weighted Magnetic Resonance Imaging

with Motion Compensation
Abstract:

Purpose: To assess and reduce signal intensity (SI) variation due to motion in multi-slice Kidney Diffusion-Weighted Imaging (DWI). Despite the use of physiological triggering schemes to limit respiratory artifacts, the presence of inhomogeneous signal dropout can induce slice-to-slice signal intensity (SI) variation in DWI. These variations were evaluated and a motion correction algorithm is presented.

Materials and Methods: SI and Apparent Diffusion Coefficient (ADC) variation between 4 consecutive slices was quantified in a phantom and sixteen volunteers. Each was scanned with three acquisitions using a single-shot SE-EPI DWI sequence. For the correction, a reconstructed set of images was rebuilt taking the maximum pixel SI from the 3 acquisitions. SI and ADC variability were compared for inter-acquisition, inter-slice, and inter-individual coefficients of variation (CV). The statistical inference between DW values and goodness of fit parameters was carried out using Friedman rank sum. The individual statistical differences were verified using Wilcoxon signed rank test.

Results: In contrast to the phantom, where all variability was <3%, a heterogeneous pattern of SI dropout was found for kidney DWI. In uncorrected DWI, inter-acquisition ADC CV was up to 23%, with 34% of slices above 10% CV. Up to 44% inter-slice SI CV was also measured. After correction, a mean reduction of 33% of the original variability between slices was obtained. Corrected inter-individual CV was under 6% in the whole population (against 9% uncorrected).

Conclusion: Significant inter-slice variability exists in renal DWI but can be reduced using a TMIP based correction.

Keywords: Kidney, Diffusion-Weighted Imaging, Motion, and Variability
Introduction:

Diffusion-Weighted Magnetic Resonance Imaging (DW-MRI or DWI) is emerging as a promising diagnostic tool for Chronic Kidney Disease (CKD), in particular for interstitial fibrosis assessment, which is a predictor of CKD evolution. In CKD patients, a significant decrease of Apparent Diffusion Coefficient (ADC) from monoexponential fitting of DW images was associated with the increase of interstitial fibrosis obtained by histopathology (1-3). Currently, the gold standard to assess interstitial fibrosis is the kidney biopsy. A major advantage of DWI, compared to biopsy, is the non-invasive assessment of the whole organ with multi-slice acquisition. However, renal multi-slice DWI remains challenging because of severe artifacts. In particular, motion artifacts impact the data analysis by degrading DW image quality. The strong diffusion encoding gradients used as a preparation make the DWI MR sequence more motion-sensitive than most other MRI sequences, even with the single-shot Echo Planar Imaging (ss-EPI) encoding scheme. In brain DW imaging, the small amount of motion from the cardiac pulsation leads to significant phase shift inducing inhomogeneous signal loss (4,5). Signal intensity loss is also particularly pronounced in cardiac DWI (6-8). In abdominal DWI, motion could arise from several sources, such as bulk subject motion, respiratory related motion, cardiac pulsation and also from bowel motion. It is safe to consider, as suggested by Elhabian et al (9), that motion artifacts are present in any given DWI acquisition. Despite the use of respiratory synchronization methods, abdominal images can still be impacted by the presence of inhomogeneous signal voids, as previously shown in liver DWI (10). An artificial elevation of ADC values in the left hepatic lobe (11) and right hepatic lobe
(12) was attributed to a direct consequence of signal void in these areas. Although motion induced signal intensity dropout is well recognized and has been described as the cause of degraded DW images quality in other organs, this effect seems to be generally neglected and vastly underestimated in renal DWI. With the growing interest in kidney DWI, particularly for the evaluation of diffuse fibrosis, the evaluation of the effect of motion as a major source of ADC variability is important. Donati et al (13) measured, in the kidney, a coefficient of variation (CV) of 10% for ADC between MR systems (CV calculated by dividing the standard deviation by the mean ADC across MR systems). Variance component analysis showed 64.6% (renal cortex) to 68.0% (renal medulla) of the ADC variability could not be attributed to the use of different vendors and field strength (13). More studies are needed to investigate the problem of signal intensity variation in kidney DWI. In particular, as a single slice, or the mean DW parameter of several slices, commonly served for the analysis, inter-slice variability is lacking in the literature.

We hypothesized that signal intensity dropout could cause significant variations of signal intensity, which will be different from one slice to the other in healthy volunteers. The goal of this study was then to demonstrate that significant slice-to-slice signal intensity variations occur in multi-slices DWI acquisition. We compared first, the inter-slice variation of DWI signal intensity and ADC in a standard ice-water phantom and then between 3 repeated DWI acquisition of healthy kidneys. A correction for these signal intensity losses was developed based on the temporal maximum intensity projection (TMIP) method developed by Rapacchi et al. (7). A motion compensation algorithm was
applied in 3 consecutive renal multi-slice DWI acquisitions to compensate the signal intensity dropout and to reduce the variability of ADC in the kidney.

Materials and Methods:

Temperature controlled ice-water phantom: An ice-water phantom served as reference to assess SI and ADC variability (between repeated DW acquisitions, and inter-slice) in a stable and reproducible manner. The ice-water phantom was scanned with the same conditions (MR system, coils and acquisition DW parameters) as for healthy volunteers. The ice-water phantom consisted of a 14mL plastic container including a 6mL polypropylene tube filled with distilled water and surrounded by water and crushed ice. The main plastic container served to reduce temperature variation during imaging acquisition. Water in the central tube was found to reach thermal equilibrium within 30 minutes of placement inside ice water container which was maintained over the course of several hours (14). The reported ADC value was ~ 1100×10^{-6} mm^2/s at around 0°C.

Healthy volunteers: This study was conducted according to guidelines of the Declaration of Helsinki and the local institutional ethical committee. Sixteen healthy volunteers, 4 females and 12 males with a mean age of 31 ± 10 years (median 28 years, range 21-66 years) were recruited after informed consent. Volunteers enrolled in this study had no known kidney or urinary disease.

MRI Protocol: Volunteers were scanned on a PRISMA 3T MR (Siemens AG, Erlangen Germany) with the standard 32-element spine coil and the 18-element phased-array abdominal coil. Three consecutive acquisitions of single-shot spin-echo Echo Planar Imaging (ss-EPI) DWI were performed with 10 coronal slices and with identical shim
setting for all DW acquisitions. The relevant DWI parameters are summarized in Table 1. The MR protocol included also a T2-weighted half-Fourier single-shot turbo spin echo (HASTE) sequence that served as reference anatomical image. HASTE was performed with the same resolution and slice orientation as the ss-EPI DWI. Renal cortical thickness was measured in a single central slice of HASTE image, in the coronal plane over a medullary pyramid, perpendicular to the capsule as in (15).

Motion compensation algorithm: An in-house motion compensation method was written in MATLAB®, incorporating a two-stage procedure. The first stage consisted of rigid registration. The second stage consisted in the compensation of Signal Intensity (SI) dropout. For the rigid registration, DW images of the 3 consecutives DWI acquisitions were registered for each of the 10 b-values and the 3 diffusion-encoding directions. Workflow of the six-step registration algorithm is presented in Figure 1. After loading the 280 DW images for each acquisition (10 slices, 10 b-values and 3 diffusion-encoding directions, except for b0), gradient images of DW images were calculated and displayed for edge detection. A mask was created to exclude the spine since during the optimization phase, the high signal intensity of the spine in gradient images could be misleading for the algorithm. The spine mask was created only on the first b0 images and propagated through the all stack images of the 3 DWI acquisitions since no motion was expected for this anatomy. From this, the registration of individual DW images (each b-value and diffusion-encoding direction separately) between the 3 DWI acquisitions was done with crossover of the gradient images. The first DWI acquisition was considered as reference. DW images of the 2 other acquisitions were (one-by-one) shifted pixel-by-pixel to maximize the gradient image product with the reference DW images. The image of
variance between images of both acquisitions was computed for a visual assessment of
the registration quality. The median displacement of the kidney between the 3 repetitive
DWI acquisitions in 2D was calculated. Mean kidney displacement was given as the
number of pixel shifted and also expressed as a percentage of the mean renal cortical
thickness over all healthy volunteers. For the second stage, from registered images,
separate diffusion direction images of the 3 DWI acquisitions were compared pixel-by-
pixel in term of SI. A reconstructed set of DW images was built pixel-by-pixel with the
highest signal intensity of the corresponding pixel of the 3 acquisitions. This resulting
new stack of DW images was referred in the manuscript as “Corrected”. Finally, the
“Corrected” DW images were saved as dicom files and OsiriX© (open source:
http://www.osirix-viewer.com) was used for the analysis with Region-Of-Interest (ROI)
placement. In the phantom, one circular ROI was drawn on the middle of the inner tube in
b₀ images and propagated through all b-values and the three directions. In volunteers, a
ROI encompassing the cortex of one kidney was drawn on 4 consecutives slices,
containing the maximum of cortex volume avoiding partial volume effect. Care was taken
to exclude susceptibility artifacts in the drawn ROI. The mean SI of all voxels in the ROI
was exported as a csv file using the OsiriX© export ROI plugin.

ADC analysis: From SI data, Apparent Diffusion Coefficient (ADC) [mm²/s] values were
obtained from a monoexponential fit of the ten b-values using the least square method.
Mean ADC values for the 3 DWI acquisitions (referred as “<DWI>” ) were calculated from
the mean SI of each b-values and directions in addition to ADC obtained from the
“Corrected” DW images. We compared SI and ADC values after our correction method
(“Corrected”), with the 3 individual repeated DWI acquisitions (referred in the manuscript as “DWI1”, “DWI2”, and “DWI3”) and the more traditional averaging method (“<DWI>"1").

Statistical analysis: SI and ADC values were reported as mean ± standard deviation of all voxels in the ROI. In a preliminary observation, normal distribution of SI and ADC values was assessed by Shapiro-Wilk test and visually, using histograms of data distribution. Due to the relative small sample size, and as non-normal distribution could not be rejected, it was decided to use non-parametric statistical tests for the following statistical analysis. SI and ADC variability, before and after correction (“Corrected” and after averaging “<DWI>"1"”), were compared inter-acquisition, inter-slice, intra-slice and inter-individual:

- Inter-acquisition ADC CV (coefficient of variation in %) was measured before correction on the 3 individual repeated DWI acquisitions. The ADC of each slice separately was measured over the 3 DWI acquisitions. The 4 slices were considered as independent. The ADC variability was measured for each volunteer, defined as the standard deviation for ADCs of the same slice over the 3 acquisitions divided by the mean ADC between the 3 acquisitions, giving 4 CVs per subject (one for each slice).

- Inter-slice SI CV was measured separately for each b-value and, for each acquisition (“DWI1”, “DWI2”, “DWI3”, “<DWI>"1"” and “Corrected”). Inter-slice SI CV for each volunteer was defined as the standard deviation of SI measured on 4 consecutives slices in a kidney divided by the mean SI over the 4 slices, resulting in 1 CV per subject for each acquisition. The consequence on ADC of inter-slice SI variability was measured via inter-slice ADC CV.
• Intra-slice variability was evaluated with the Root Mean Squared Error (RMSE) included in the goodness of fit toolbox available in MATLAB®. The best regression was defined as the one with the RMSE closest to zero. Thus, the deviation of fitted to measured data (signal intensities of each of the three DWI repetitions, “<DWI>”, and “Corrected”) was minimum.

• Inter-individual ADC CV was measured as the standard deviation of ADCs over the 16 volunteers divided by the mean ADC (over 4 slices) between volunteers, yielding 1 CV for the whole population for DWI1, DWI2, DWI3, “<DWI>,” and “Corrected”.

The statistical inference between DW values and goodness of fit parameters (RMSE and $R^2$) was carried out using Friedman rank sum statistical test. The individual statistical differences were verified using Wilcoxon signed rank test (paired data). A p-value of less than 0.05 was considered to indicate statistical significance. Statistical analyses were performed using the stats R software version 0.98.1091 and PMCMR package to calculate Pairwise Multiple Comparisons of Mean Rank Sums.

Results:

Temperature controlled ice-water phantom:

A homogeneous image with no focal signal intensity loss was observed in the ice-water phantom. The constant SI measured in the ice-water phantom, over repeated DWI acquisitions and between slices for all b-values, with all CVs (inter-acquisition and inter-slice) around 3%, supported this qualitative observation. Inter-slice CVs of the ice-water phantom are shown in Figure 2 (light grey). Resulting ADC values were constant
between the 3 repeated DWI acquisitions with ADC inter-acquisition variability of 2%±0.1%.

**Variability of renal diffusion image variability in volunteers before correction:**

In contrast with the ice-water phantom, a heterogeneous pattern of localized signal dropout was visible within different areas of the healthy parenchyma in DW images of all volunteers. As illustrated in Figure 3, with 3 consecutive slices of the DWI acquisition in one volunteer, these SI losses were randomly distributed, without a reproducible SI void pattern between slices, acquisitions, b-values or DW encoding directions. SI losses yielded an inhomogeneous ADC map with artificial hyperintense signal areas.

- **Inter-acquisition variability:**

Signal dropout was also visible within different areas of the parenchyma between repeated DW acquisitions. Figure 4 shows an example of the same coronal slice acquired in 3 consecutive DWI acquisitions for one volunteer. Repetition of the same DWI acquisition (3 times) gave a mean ADC inter-acquisition CV over the 16 volunteers of 8%±5% [range, 1-23%] with 34% of slices above 10% variability.

- **Inter-slice variability:**

Figure 2 shows inter-slice SI variation in healthy volunteers, before correction, together with comparison of SI variation in the ice-water phantom. Compared to the SI variation measured in the phantom, an increase of inter-slice CV was measured in volunteers. The CV is also increasing with increasing b-value. A minimum inter-slice SI CV was measured for the b-value of 10s/mm² (CV 5±3%, range 3-18%), whereas the maximum inter-slice SI CV was measured for b-value of 900s/mm² (CV 14±8%, range 5-44%). All resulting
inter-slice ADC CV values are displayed in Figure 5. Inter-slice ADC CV were not significantly different between the 3 repeated DWI (all p-values > 0.05, as shown in Figure 5).

- Intra-slice ADC variability:

Figure 6 shows boxplot of RMSE values before correction. No RMSE differences were measured between the 3 repeated DWI acquisitions.

- Inter-individual variability:

Mean ADC values \([10^{-6}\text{mm}^2/\text{s}]\) in the whole population (measured for all volunteers and over 4 consecutive slices) were 2323±188 for “DWI1”, 2361±190 for “DWI2”, and 2316±199 for “DWI3”. The associated inter-individual CV were 8%, 8% and 9% for “DWI1”, “DWI2” and “DWI3” respectively.

**Motion compensation algorithm:** The mean cortical thickness measured on HASTE images was 5.0±0.8mm [range, 3-6mm]. An edge translation of at least one pixel (2mm×2mm), which represents 40% of the cortical thickness, was measured in 66% of the 280 DW images, with 26% for x-translation and 41% for y-translation. Registration of DW images from the 3 reference DWI acquisitions was therefore a prerequisite for SI dropout compensation. Kidney motion (displacement between 3 repeated DW acquisitions) was estimated with a median over all DW images (280 per acquisitions) of 0.5 pixels for x-translation (up to 9 pixels) and 1 pixel (up to 6 pixels) for y-translation.

**Reduction of renal diffusion image variability in volunteers after correction:**

Visually, the parenchyma of the “Corrected” DW images was more homogenous, with less SI loss, compared to the 3 repeated DW acquisitions shown in Figure 3.
reduction of SI loss in “Corrected” DW images was associated with the reduction of hyperintense pixels on the ADC map, which would indicate overestimated ADC values.

- Inter-slice variability:

Inter-slice ADC variability was reduced by compensating DW images for signal loss. In particular, CV was decreased by more than 50% between “Corrected” ADC and ADC from the 3 repeated DWI and the reduction was 37% compared to “<DWI>$. Significant differences between groups were measured for inter-slice ADC CV ($p=4\times10^{-6}$) with a Friedman test ($\chi^2=30$, df=4). In particular, a significant reduction of ADC inter-slice variability was measured with “Corrected” DW images compared to “<DWI>$"$, and to all 3 repeated DWI acquisitions (Figure 5). There was also a significant difference between the 3 repeated DWI and “<DWI>$"$ values ($p=1\times10^{-5}$) with Friedman test ($\chi^2=28$, df=4). However, this difference was not statistically different for all 3 repeated DWI acquisitions, as shown in Figure 5.

- Intra-slice variability:

Reduction in SI variations leads to a more robust fitting measured by RMSE. In particular, significant differences for repeated measures within corrected, “<DWI>$"$, and non-corrected DWI acquisitions were measured for RMSE ($p=6\times10^{-5}$) with Friedman ($\chi^2=25$, df=4). There was a significantly lower RMSE for the fit function in “corrected” SI compared to data from the 3 repeated DWI acquisitions ($p=9\times10^{-5}$ for comparison with “DWI1”, $p=0.001$ for comparison with “DWI2”, and $p=0.0002$ for comparison with “DWI3”) (Figure 6). Also, a significantly lower RMSE was measured with corrected SI compared to “<DWI>$"$ ($p=0.03$). “<DWI>$"$ was associated to a significantly lower RMSE compared to
non-corrected SI in 2 out of 3 acquisitions (respectively p=0.002 and p=0.02), and almost significant in one acquisition (p=0.05).

- **Inter-individual variability:**

Mean ADC values [$10^{-6}$ mm$^2$/s], measured on all volunteers and over 4 consecutive slices were 2143±126 for “Corrected” DWI, 2344±198 for “<DWI>”, as shown in Figure 7. A reduction of 33% variability between slices, measured with CV in each volunteer individually, was obtained with the corrected method. The corrected method resulted in less inter-individual CV in the whole population with a decrease of inter-individual CV for “Corrected” under 6%. Whereas, inter-individual CV for “<DWI>” was in the same order than inter-individual CV of the 3 repeated DWI at 9%.

**Discussion:**

Multi-slice renal DWI suffers from ADC variability between slices and between acquisitions as a result of signal intensity dropout in DW images. We proposed a method to correct for this. The amplitude of this variability was measured in healthy volunteers with coefficients of variation. Despite the use of a prospective respiratory navigator in the acquisition scheme, residual motion degraded kidney DW image quality. A mean of 10%, up to a maximum of 44% signal intensity variation was observed between slices. 10% is typically the same order of magnitude as the ADC difference between the cortex and the medulla of healthy volunteers (16,17). Any changes between these two distinct tissues could simply be missed without compensation for signal dropout. Compensation for motion is therefore important for reliable measurement of early pathologies leading to small
variations. The signal dropout phenomenon is well known in diffusion MRI and considered as “all-or-none” (6). All physiological motion can potentially lead to variability in DWI by inducing signal intensity dropout in DWI images. DWI is sensitive to motion of the order of tens of microns, and physiological motion could induce displacements on the order of millimeters. Molecular diffusion of water in the tissue is therefore about several orders of magnitude smaller than physiological motion. Even a relatively “small” confounding physiological motion could directly impact DWI. Although respiratory motion is suspected to be the most problematic, motion may also be derived from other sources, such as blood flow pulsatility and intestinal peristalsis. Breath hold acquisitions were not used in this study. ADC from breath hold DW images has been reported to be less well correlated to eGFR than ADC from PACE DW images in a study of split renal function assessment (18). In this previous study, the authors found that PACE DW images had higher signal-to-noise and contrast-to-noise ratios than breath hold DWI, as well as a higher diagnostic value in predicting a reduction in split renal function measured by area under the receiver operator curve. In addition, in a pilot study (data not shown), slice-to-slice ADC variability was also measured during breath hold acquisition, which suggested that blood flow pulsatility and intestinal peristalsis could not be neglect. Several studies have shown that cardiac motion could also impact DW parameters in the liver by inducing bulk motion (11,19,20). In kidney DWI, the use of double triggering for respiratory and cardiac has also been considered to minimize also the influence of blood flow pulse effects (21-23). However, these analyses were limited to a single slice. There is no penalty in acquisition time to do multi-slice acquisition as this fits in the respiratory-gated TR. The multi-slice acquisition offers full kidney assessment, which is useful for
evaluation of local pathologies. In the present study, double cardiac and respiratory synchronization was not used because of the prohibitive acquisition time. Further study to define the respective importance of all the possible physiological motion on renal DWI will be needed since it was beyond the scope of the present work which was to correct for the signal dropout.

To counteract the motion problem in DWI, several studies have incorporated motion-compensated diffusion gradient waveforms to address the signal dropout in cardiac DWI due to myocardial motion (24-28). The original diffusion gradient waveform used was replaced by second-order motion-compensated gradients for acceleration-compensated (27,28). These techniques, limiting the effect of contractile heart motion on ADC, although very promising, required dedicated MR sequences not available as a commercial product at the time of the study.

In this study, a method using three temporal repetitions of the DWI acquisition was proposed to compensate for signal dropout, at multiple b-values, caused by motion during diffusion encoding. This compensation method was based on temporal maximum intensity projection (TMIP), as developed for cardiac DWI (7,8,29,30). Cebral et al (29) used this method to reconstruct cerebral arteries from the 4D phase-contrast MR acquisition. They combined the magnitude images of each phase in cardiac cycle by taking maximum intensity of each voxel. TMIP in cardiac DWI was associated with an optimal time-window for the cardiac DWI acquisition. The heterogeneous pattern of signal dropout was reduced for more uniform cardiac muscle DWI, compared to traditional cardiac DWI without motion compensation (7,8,30). In addition, motion compensation, using TMIP, has the clear advantage of being easily implemented with all DW sequences
available on the clinical MR systems. However, a limitation is the longer total exam time, since the proposed motion compensation method requires multiple DWI acquisitions with the assumption of every pixel being free of signal dropout in at least one of the repeated DW acquisitions. However, multiple acquisitions in DWI are commonly performed in clinical routine to enhance signal-to-noise ratio by averaging. As we have shown in our study, averaging is far less efficient than using TMIP to compensate for signal variations. Therefore, TMIP should be considered instead of averaging for renal DWI.

The main clinical impact of the present work is to emphasize the potential variability in renal DWI that could be encountered in patients and to propose a solution to reduce it. Several renal pathologies, such as renal tumors (31), acute ureteral obstruction (32), kidney injury (33) and pyelonephritis (34) as well as interstitial fibrosis (35) have been shown to induce a decrease of ADC. The presence of such pathologies could be missed in DWI if they do not consider and compensate motion, as resulting signal dropout can lead to artificial overestimation of ADC values. In addition, there is no reference ADC value for healthy volunteers because of the wide range of different ADC values measured across different studies and even in same studies across volunteers. In this context it is difficult to compare studies and all sources of variability have to be minimized. Our correction method may help to obtain more robust DWI allowing definition of normal reference ADC value. Nevertheless, the clinical benefit of compensation for signal dropout induced by motion should be tested in renal disease DWI assessment.

In conclusion, the present study first showed a significant variability in renal ADC measurements and then proposed a method to reduce the ADC variability between
consecutives slices and therefore between the subjects by compensating for signal dropout.
References:


Table

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Table 1: Imaging parameters for the three single-shot SE-EPI DWI
Figure Legends

Figure 1: Image processing workflow with the six steps of the registration algorithm

Figure 2: The bar chart shows inter-slice coefficient of variation (CV, expressed in %, for each b-value. In light grey, CV was measured in the center of the ice-water phantom across 3 consecutive DWI acquisitions. Bars represent the standard deviation between slices. All slice-to-slice CV was less than 3% in the ice-water phantom. In dark grey, CV was obtained in the cortex of 4 consecutive slices averaged for 16 volunteers. Bars represent the standard deviation between the mean CV of the 16 volunteers.

Figure 3. Example of 3 consecutive slices (A, B, C) of coronal single-shot SE EPI DWI of one 39 year old healthy volunteer kidneys, with associated ADC map (last column). The 4 columns correspond to the last 4 b-values images: b=300 s/mm$^2$ (first column), b=500 s/mm$^2$ (second column), b=700 s/mm$^2$ (third column), and b=900 s/mm$^2$ (fourth column). White arrows point to areas impacted by localized signal intensity dropout in different parts of the kidney. Within white frame, a global signal intensity dropout affected the whole left kidney. Signal dropout in DWI caused hyper signal area in ADC map.

Figure 4: Example of the same coronal single-shot SE EPI DWI acquired on 3 consecutive acquisitions (A, B, C) in one 26 year old healthy volunteer kidneys, with associated ADC map (2nd row). The parenchyma of the corrected DW image (D) is more homogenous compared to the 3 standard DW acquisitions, resulting in less hyper signal area on the associated ADC map.
Figure 5. Inter-slice ADC variability measured in 4 consecutive center slices of the renal cortex DWI of 16 healthy volunteers. Significant reduction of ADC slice-to-slice variability in “Corrected” compared to ADC was measured with averaging the 3 DWI acquisitions “<DWI>_i”, as well as, compared with non-corrected DWI.

Figure 6. Root mean squared error (RMSE) values for the 4 consecutives center slices of the 16 healthy volunteers. RMSE of “Corrected” SI was always significantly lower compared to the average of the 3 DWI acquisitions “<DWI>_i” and repeated DWI acquisitions.

Figure 7: Boxplot illustrating the mean ADC values [10^-6 mm^2/s] measured in 16 healthy volunteers (one ADC for each volunteer, averaging over 4 consecutive slices). Significant reduction of ADC values was measured in “Corrected”, compared to the average of the 3 DWI acquisitions “<DWI>_i” and non-corrected (3 repetitives DWI acquisitions).
Image processing workflow with the six steps of the registration algorithm

676x507mm (72 x 72 DPI)
The bar chart shows inter-slice coefficient of variation (CV, expressed in %, for each b-value. In light grey, CV was measured in the center of the ice-water phantom across 3 consecutive DWI acquisitions. Bars represent the standard deviation between slices. All slice-to-slice CV was less than 3% in the ice-water phantom. In dark grey, CV was obtained in the cortex of 4 consecutive slices averaged for 16 volunteers. Bars represent the standard deviation between the mean CV of the 16 volunteers.
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**p=3 x 10^-5**
**p=0.00077**
**p=0.00043**
**p=6.1 x 10^-5**
*p=0.0042*
*p=0.0027*
*p=0.058*
*p=0.86*
*p=0.37*
*p=1.18*

Inter-slice ADC variability measured in 4 consecutive center slices of the renal cortex DWI of 16 healthy volunteers. Significant reduction of ADC slice-to-slice variability in “Corrected” compared to ADC was measured with averaging the 3 DWI acquisitions “<DWI>i”, as well as, compared with non-corrected DWI.

620x467mm (72 x 72 DPI)
Root mean squared error (RMSE) values for the 4 consecutives center slices of the 16 healthy volunteers. RMSE of "Corrected" SI was always significantly lower compared to the average of the 3 DWI acquisitions "<DWI>1" and repeated DWI acquisitions.

628x419mm (72 x 72 DPI)
Boxplot illustrating the mean ADC values [10^-6 mm^2/s] measured in 16 healthy volunteers (one ADC for each volunteer, averaging over 4 consecutive slices). Significant reduction of ADC values was measured in "Corrected", compared to the average of the 3 DWI acquisitions "<DWI>_i" and non-corrected (3 repetitives DWI acquisitions).
3 Conclusion and Perspectives
3.1 Main conclusions

Throughout this thesis DWI was explored for assessment of kidney interstitial fibrosis. The goal was to overcome the difficulties encountered in vivo, by proposing new methods for renal DWI. Home made phantoms and a translational approach were adopted for the optimization of the technique, before validation in healthy volunteers and CKD patients. The introduction of RESOLVE in renal DWI as well as the implementation of new tools to provide more robust DW quantification has been proposed. In particular, the use of $\Delta$ADC and compensation of physiological motion were of major importance to reduce errors and pitfalls encountered in renal DWI.

The first achievement was the implementation of the RESOLVE sequence for kidney imaging (first publication [28]). RESOLVE was proposed to limit EPI artefacts and improved DW image quality. The implementation of the RESOLVE sequence for kidney DWI required a homemade adaptation of a respirator gating system, through the small imaging system. The improvements in kidney DW image quality obtained with the RESOLVE strategy against was compared to traditional single-shot EPI. Post-processing tools, in addition to the traditional overall preference by a radiologist, were proposed to quantify the improvements. The RESOLVE sequence was then used in protocol for small animal models of interstitial fibrosis. We assessed the sensibility of ADC with this strategy to differentiate pathology from healthy tissue in a moderate and severe small animal models of interstitial fibrosis. We overcame the challenge of scanning small animal models in clinical systems with a DW sequence, prone to severe artifacts. In chronic kidney patients, a comparison of ADC and the cortico-medullary $\Delta$ADC from RESOLVE was done in comparison to T1 and $\Delta$T1 from T1 mapping, another MRI sequence frequently used in cardiac evaluation of interstitial fibrosis. It was the first time that these 2 MRI methods were compared in kidney fibrosis assessment. This second achievement has been published in a second paper [26]. A major interesting point of this paper was the use of the RESOLVE strategy in CKD patients with histological validation. $\Delta$ADC improved fibrosis assessment by comparison to cortical and medullary ADC alone. Also, a negative $\Delta$ADC was found in all patients with more than 40% of interstitial fibrosis, suggesting feasibility of the introduction of this threshold as predictor for renal fibrosis. In addition, a multi parametric study was proposed with the use of multi-linear regression to combine ADC and T1 in a single statistic to improve renal fibrosis assessment. In kidney, previous multi parametric studies evaluated MR parameters individually. I proposed to incorporate all in one in order to improve the correlation with two independent aspects of interstitial fibrosis. This work received the ISMRM Magna Cum Laude Merit Award at the ISMRM 24th annual meeting.

Despite the significant improvement achieved with RESOLVE, the time penalty inherent of this strategy (about 5 times longer than single-shot EPI in our case) was a limiting factor for its used in clinical practice. During the thesis I learnt among other things that it is not because images look pretty that they have any interest for the diagnosis and patient care. This interesting point motivated our study of comparison between RESOLVE and single-shot EPI for renal fibrosis assessment. It was interesting to notice also that the b-values sampling and fitting model had its importance. We used an ADC with 10 b-values, which was rather unusual as a monoexponential could be fitted with a minimum of 2 b-values. The number of b-values was motivated by the fact that reducing the number of b-values by 2, or removing the small b-values causes a loss of prognostic power with a significant reduction of $R^2$. RESOLVE became a sequence of choice in our institute for the evaluation of prostate by DWI. However, some persisting difficulties remained in the renal application. We wanted first to validate the reproducibility of $\Delta$ADC on all MR systems of HUG (paper in preparation). No difference in ADC was measured in phantom. Variations were measured in healthy volunteers. These variations were minimized with the use of the $\Delta$ADC index. An important limitation of the ADC use in clinical routine is the absence of ADC threshold for diagnosis. Despite the interesting threshold of 40%, from the second publication, an important variability persisted in patients with the same level of interstitial fibrosis. A significant variability was measured in healthy volunteers also. Physiological effects could be minimized with the use of $\Delta$ADC. Moreover, it is well known that motion degraded image quality and the robustness of the ADC. This phenomenon is currently a major challenge in cardiac DWI. However it was largely unreported in kidney where the potential of multi-slice DW images is untapped and
a single slice is often analysed. However, an important aspect of DWI compared to biopsy is the potential assessment of the whole kidney. I evaluated the variability between slices and between volunteers before proposing a compensation method to reduce this variability.

3.2 Importance of the thesis project for the clinician and patient care

The interest of this thesis project was confirmed by the clinician enthusiasm. Indeed, the absence of gadolinium-contrast injection in our protocol was extremely valuable, particularly in the CKD population making its clinical acceptance very likely. Altogether the methodology proposed in this thesis has a strong potential to improve follow up and care of CKD patients. The major potential application on everyday clinical practice would be to predict the level of fibrosis in CKD by identifying at high-risk patients with the threshold of 40% interstitial fibrosis. The goal would be to avoid unnecessary serial biopsies, particularly in diabetic or hypertensive vascular patients who do not usually benefit from biopsy because of complications. Patients harbouring acute or chronic kidney disease may undergo non-invasive MR imaging and blood/urine tests to determine the extent of interstitial fibrosis and to tailor the treatment adequately without the need for a kidney biopsy. Our protocol may be first used as a follow up tool in patients where diagnosis was already established by biopsy. The nephrologist may therefore tailor therapy non-invasively and adapt treatment in the case of extensive fibrosis, for example. In addition, the use of multi-slice imaging may help to assess structural kidney modifications locally and more accurately. If renal DWI is validated as a prognostic tool (with or without biomarkers) in CKD patients, it may be of great value in the future to identify patients at risk of progression and to follow their evolution under classical or experimental new emerging therapies.

3.3 Future perspective to overcome the limitations

To efficiently measure kidney interstitial fibrosis with MRI, there are some challenges that still need to be overcome. Obviously, these first experiments have to be confirmed, in particular in a larger cohort of non-homogenous patients. The multiparametric study, with T1 and ADC, showed the potential of combining several biomarkers to assess more precisely kidney fibrosis. A non-invasive score must be validated against biopsy in a large population of kidney pathologies with the coupling of the several biomarkers. The addition of non-MRI biomarkers will also help to identify precisely the interstitial fibrosis from others pathologies. ADC is very sensitive as we showed, however, this specificity should be improved. All pathologies inducing a decrease of interstitial space would lead to a decrease of ADC. Consequently, we need to identify and isolate other pathologies, not necessarily linked to interstitial fibrosis, that could also induce a decrease of ADC. For that point, dividing patients into subgroups will help. Separation according to the level of inflammation, vascular injury, and oedema needs to be performed. Since ADC is sensitive to every effects on the extracellular space, a clear understand of this factors is of major importance. Also, we need to understand which part the perfusion effect plays in the measured ADC. Experiments showed that removing the small b-values would decrease the R². It would be interesting to include perfusion evaluation in our population, such as Arterial Spin Labeled (ASL) to evaluate the perfusion and integrate this information in an MLR of ASL and ADC at high b-values. I recommend that all renal DWI should be compensated for motion and a more adapted fit and b-values should be used. With a better understanding of the perfusion effect combined with an efficient correction of motion, we should be able to decrease the number of b-values efficiency.

In conclusion, this thesis demonstrated the feasibility of measuring renal interstitial fibrosis more reliably by addressing and minimizing sources of variability and pitfalls.

References


4 Appendix: curriculum vitae
MRI Physicist

PhD student in MRI physics, (November 2012 - )
Title: Renal Fibrosis Assessment by Diffusion-Weighted Magnetic Resonance Imaging
Thesis supervisors: Pr. J.-P. Vallée (Division of Radiology, Geneva University Hospitals) and Pr. J.-P. Wolf (Biophotonics Group, University of Geneva)

- Research work mainly focused on pre-clinical and clinical validation of novel quantitative MRI methods for chronic kidney disease assessment

Participation in the European FP7 NanoDiaRA Project on Rheumatoid Arthritis and Osteoarthritis
- Iron Oxide Nanoparticles (SPION) as contrast agents and quantitative MRI in small animal models

MRI Skills:

- Protocol optimisation and MRI acquisitions for research protocols (Siemens, Philips)
- Quantitative MRI (Diffusion-Weighted Imaging (DWI), T1-, T2- and T2* Mapping)
- Image processing, image analysis and statistical analysis

Other Skills:

- Languages: French (mother tongue), English (fluent)
- Computer skills: OsiriX, Matlab, R, ImageJ, SPSS, LaTeX
- Ability to work in interdisciplinary environment (radiologist, nephrologist, physicist)

QUALIFICATION and RESEARCH EXPERIENCE

MSc degree in Physics, University of Strasbourg, France
- Radiation Physics, Detector, Instrumentation and Imagery (2011-2012)
- Subatomic Physics and Astroparticles (2010-2011)

Continued education:

RESAL: LTK Module 1 Swiss Authorization in vivo studies, Lausanne, Switzerland
Course in Laboratory Animal Science accredited by the Federation of European Laboratory Animal Science Associations (FELASA accreditation Nr. 38/12)
Study projects:

Master Internship in Particle Physics (2012, 5 months)
Supervisor: Dr C. Jollet and Dr A. Meregaglia, Hubert Curien Institute, University of Strasbourg, France
Study of muon-induced background in the Double Chooz experiment
Programming: C++, ROOT

Master Internship in Particle Physics (2011, 4 months)
Supervisor: Pr. A. Nomerotski, Physics Department, University of Oxford, UK
Characterization of PmMS Monolithic Active Pixel Sensor for Imaging Mass Spectrometry
Programming: LabVIEW

Theoretical Internship in Particle Physics (2010, 4 months)
Supervisor: Dr. B. Fuks, Hubert Curien Institute, University of Strasbourg, France
Symmetry breaking in the Standard Model

Exchange Project with University Politechnika of Wroclaw, Poland (2007, 1 month)
Experimental work with Laser and Workshop on quantum dots

AWARDS and DISTINCTION

ISMRM Magna Cum Laude Merit Award for the work entitled:
Multiple Linear Regression for Predicting Fibrosis in the Kidney using T1 Mapping and RESOLVE Diffusion-Weighted MRI, presented at the ISMRM 24th Annual Meeting, Singapore 2016

STIPEND Award for Annual ISMRM 2017 Meeting, Honolulu, HI, USA 2017

TEACHING EXPERIENCE

Teaching Assistant (2012-2016)
Co supervision of bachelor students (medicine and medical imaging technologist)
University of Geneva and Haute Ecole de Santé, Geneva, Switzerland

ADDITIONAL INFORMATION

Sales assistant (2004-2010)
Various retail outlets (Camaieu, Minelli, Darjeeling, Brice, Armand Thiery)

Other interests including: travelling, world food at home and abroad, running (Lausanne half marathon 2016 in 2:13)
PUBLICATIONS

Peer reviewed journal papers:


International conference proceedings:

International Society for Magnetic Resonance Medicine (ISMRM), 2017, Honolulu, HI, USA

Posters

• Friedli I, Crowe LA, Delattre, B MA, de Perrot T, Martin PY, de Seigneux S, Vallée JP; The Cortico-Medullary ADC Difference reduces inter-system variability in Renal Diffusion-Weighted Imaging

• Crowe LA, Montecucco F, Carbone F, Friedli I, Hachulla AL, Braumersreuther V, Mach F,Vallée JP; 4D cine strategy for assessment of mouse cardiac function and infarct size in a single acquisition optimized for a clinical 3T MR system

International Society for Magnetic Resonance Medicine (ISMRM), 2016, Singapore

PowerPitch

• Friedli I, Crowe LA, Berchtold L, Moll S, Hadaya K, de Perrot T, Martin PY, de Seigneux S, Vallée JP; Multiple Linear Regression for Predicting Fibrosis in the Kidney Using T1 Mapping and RESOLVE Diffusion-Weighted MRI (Magna Cum Laude prize for the power pitch)

Posters

• Friedli I, Crowe LA, De Seigneux S, Vallée JP; Assessment of Variation Induced by Physiological Motion in Multi-Slice Renal Diffusion-Weighted MRI at 3T

• Orci L, Oldani G, Lacotte S, Slits F, Friedli I, Wirth W, Vallée JP, Tos C, Crowe LA; Quantitative Assessment and Follow-Up of Hepatocellular Carcinoma in Rat Livers Using Clinical 3T MRI

International Society for Magnetic Resonance Medicine (ISMRM), 2015, Toronto, Canada

Posters

• Friedli I, Crowe LA, Berchtold L, Moll S, Hadaya K, De Perrot T, Martin PY, De Seigneux S, Vallée JP; Non-Invasive Assessment of Fibrosis and Inflammation in the Whole Kidney of CKD Patients by Diffusion-Weighted Imaging with Readout-Segmented EPI

• Friedli I, Crowe LA, Berchtold L, Moll S, Hadaya K, Martin PY, De Seigneux S, Vallée JP; Non-Invasive Assessment of the Whole Kidney by MOLLI T1 Mapping in Chronic Kidney Disease Patients
• Crowe LA, **Friedli I**, Vesin C, Berchtold L, Martin PY, De Seigneux S, Vallée JP; Non-Invasive Assessment of Fibrosis and Inflammation in Rat Kidney Models with Diffusion-Weighted MRI

• De Perrot T, Delattre BMA, Crowe LA, **Friedli I**, Fusztaeszeri M, Tille JC, Iselin C, Vallée JP; Multi-B-Value Diffusion Weighted Imaging Acquired on a 3T MR Scanner: Comparison of the Apparent Diffusion Coefficient in Prostate Cancer Detection and the Contribution of B-Value Images in ADC Map Interpretation

International Society for Magnetic Resonance Medicine (ISMRM), 2014, Milan, Italy

Posters

• **Friedli I**, Crowe LA, Viallon M, De Seigneux S, Vallée JP; Improvement of Renal Diffusion-Weighted MR Imaging with Readout-Segmented Echo Planar Imaging at 3T.

• Crowe LA, Kunz N, **Friedli I**, Gramoun A, Grosdemange K, Corum CA, Gruetter R, Vallée JP; SWIFT positive contrast technique for rat knee bone imaging at 14 T


Swiss Radiology Society, 2017, Bern

Oral Presentations

• **Friedli I**, Crowe LA, Delattre, B MA, de Perrot T, Martin PY, de Seigneux S, Vallée JP; The Cortico-Medullary ADC Difference reduces inter-system variability in Renal Diffusion-Weighted Imaging

Swiss Radiology Society, 2016, Davos

Oral Presentations

• **Friedli I**, Crowe LA, de Seigneux S, Vallée JP; Assessment of variation induced by physiological motion in multi-slice renal diffusion-weighted magnetic resonance imaging at 3T

• **Friedli I**, Crowe LA, Berchtold L, Moll S, Hadaya K, de Perrot T, Martin PY, de Seigneux S, Vallée JP; Multiple linear regression for predicting fibrosis in the kidney using T1 Mapping and RESOLVE diffusion-weighted magnetic resonance imaging (MRI)

• Crowe LA, Montecucco F, Burger F, Roth A, Carbone F, **Friedli I**, Hachulla AL, Braunschreuther V, Mach F, Vallée JP; Simultaneous Assessment of Cardiac Function and Infarct Size in a Mouse Model Using a 4D Strategy on a Clinical 3T MR System

Swiss Radiology Society, 2015, Basel

Oral Presentations

• **Friedli I**, Crowe LA, Berchtold L, Moll S, Hadaya K, Vesin C, de Perrot T, Martin PY, de Seigneux S, Vallée JP; Non-invasive assessment of fibrosis and inflammation in the whole kidney of CKD patients by diffusion-weighed magnetic resonance imaging with readout-segmented EPI

Poster

• Crowe LA, **Friedli I**, Vesin C, Berchtold L, Martin PY, de Seigneux S, Vallée JP; Non-invasive assessment of fibrosis and inflammation in rat kidney models with diffusion weighted (poster prize)

Swiss Radiology Society, 2014, Montreux

Oral Presentations

• **Friedli I**, Crowe LA, Viallon M, de Seigneux S, Vallée JP; Improvement of renal diffusion-weighted MR imaging with readout-segmented echo-planar imaging at 3T

• Crowe LA, Kunz N, **Friedli I**, Gramoun A, Grosdemange K, Corum CA, Gruetter R, Vallée JP; SWIFT MRI bone imaging for rat knee joint destruction assessment at 14T
Poster