Kidney oxygenation under pressure

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A tri-exponential model for intravoxel incoherent motion analysis of the human kidney: in silico and during pharmacological renal perfusion modulation

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*Authors contributed equally

Abstract

In the kidneys, there is both blood flow through the capillaries and flow of pre-urine through the tubuli and collecting ducts. We hypothesized that diffusion-weighted (DW) MRI measures both blood and pre-urine flow when using a tri-exponential intravoxel incoherent motion (IVIM) model. Our aim was to systematically investigate and optimize tri-exponential IVIM-analysis for the kidney and test its sensitivity to renal perfusion changes in humans.

The tri-exponential fit probes the diffusion coefficient ($D$), the intermediate ($D^*$) and fast ($D^{**}$) pseudo-diffusion coefficients, and their signal fractions, $f_D$, $f_i$ and $f_f$. First, we studied the effects of fixing the $D^*$-coefficients of the tri-exponential fit using in silico simulations. Then, using a 3T MRI scanner, DW images were acquired in healthy subjects (18–24 years) and we assessed the within-subject coefficient of variation (wsCV, $n=6$). Then, renal perfusion was modulated by Angiotensin II infusion during which DW imaging of the kidneys and phase contrast MRI of the renal artery was performed ($n=8$). Radioisotope clearing tests were used to assess the glomerular filtration rate.

Simulations showed that fixing the $D^*$-coefficients could potentially increase the fit stability, in fact decreased the precision of the model. Changes in $D^*$-coefficients were translated into the $f$-parameters instead. Fixing $D^*$-coefficients resulted in a stronger response of the fit parameters to the intervention. Using this model, the wsCVs for $D$, $f_D$, $f_i$ and $f_f$ were 2.4%, 0.8%, 3.5%, 19.4% respectively. $f_i$ decreased by 14% ($p=0.059$) and $f_f$ increased by 32% ($p=0.004$) between baseline and maximal Angiotensin II dose. $f_f$ inversely correlated to renal plasma flow ($R=-0.70$, $p<0.01$) and $f_i$ correlated to glomerular filtration rate ($R=0.39$, $p=0.026$).

We validated kidneey-specific method for IVIM analysis using a tri-exponential model. The model is able to track renal perfusion changes induced by Angiotensin II.
INTRODUCTION

Traditionally, intravoxel incoherent motion (IVIM) analysis of diffusion weighted (DW) MRI employs a bi-exponential decay model to distinguish between capillary perfusion and tissue diffusion fractions. 1,2 Since its introduction, IVIM modelling has been applied to human kidneys, e.g. to identify altered perfusion in native kidney lesions and hypoperfused regions in transplanted kidneys. 3-7 However, as Muller et al 33 already noticed, the kidneys are rheologically more complex than other organs and a bi-exponential model may not be sufficient to model renal physiology.

In the kidneys, there is both perfusion of the blood vessels (including the glomeruli; which is traditionally assessed as renal plasma flow, RPF) and flow of pre-urine through the tubuli and collecting ducts (with glomerular filtration rate -GFR- as its closest measurable proxy). Therefore, the usual bi-exponential IVIM model is less suited for application in kidney MRI data. 3 Incorporating a third exponent in the IVIM model could solve this problem. Such a model could potentially enable discrimination between blood and pre-urine flow. Recently, it was shown by Van Baalen et al. 5 that such a tri-exponential IVIM model may be preferable in the kidney. In their implementation, the tri-exponential model produced three distinct signal fractions: a diffusion fraction, an intermediate bulk motion fraction (f) and a fraction of fast bulk motion (f). In a group of ten healthy subjects the distributions of these fractions were shown to be consistent with the distinct functional regions within the kidney. 8 However, there are two aspects that remain unclear. One, whether the tri-exponential model can be optimized by fixing either one or both pseudo-diffusion parameters or not and, two, how this model relates to changes in kidney perfusion.

As for the first aspect, the classic bi-exponential IVIM model fit, the parameters related to perfusion have a limited reproducibility. Therefore, to improve the robustness of an IVIM model the pseudo-diffusion coefficient (D*) is usually fixed. 1,9,10 However, when one or, in case of a tri-exponential model, two D*’s are fixed, information on these parameters is lost and variation in these parameters may be transferred to the signal fraction parameters (f, f). Therefore, before applying such a model on physiological data, the effects of fixing pseudo-diffusion coefficients on the reproducibility of the tri-exponential IVIM model should be assessed.

To explore the model’s sensitivity to changes in renal perfusion, we reduced renal perfusion pharmacologically by continuous Angiotensin II (Ang II) infusion. As a product of the renin angiotensin system (RAS), Ang-II infusion mimics the effects of RAS activation as is common in CKD patients. 11 The renal specific effects of Ang II include a perfusion reduction (GFR and RPF decrease), while filtration pressure is increased by selective vasoconstriction of the
efferent glomerular arterioles. Also, tubular sodium resorption is increased and water is retained. If tri-exponential IVIM analysis is sensitive to changes induced by Ang II infusion, the technique may be suitable for clinical renal hemodynamic assessment.

For these reasons, we tested the following hypotheses 1) fixing $D^*$’s improves the tri-exponential IVIM model of the kidney in terms of reproducibility and sensitivity and 2) the tri-exponential IVIM model is sensitive to pharmacologically induced changes in renal perfusion. To test hypothesis 1, we investigated the reproducibility of the IVIM-fits using in silico simulations and in vivo repeated measures. To test hypothesis 2, we obtained IVIM, kidney perfusion and GFR data in healthy volunteers in whom we reduced renal perfusion and GFR by staged Ang-II infusion.

**MATERIALS AND METHODS**

MRI scans were performed in two groups of healthy volunteers (group A: n=6, age 19 – 22 years, 5 males and group B: n=8, age 18 – 24 years, 5 males). In total, the MRI data were acquired during four sessions, each session on a different day. In session 1, group A was scanned four times without repositioning, to test intra-session reproducibility. Sessions 2 and 3 (group B) consisted of a single scan to determine inter-session repeatability of the model. Finally, in session 4 (group B) subjects were scanned at baseline and during three increasing doses of continuous intravenous Ang-II infusion. After the Ang-II MRI protocol, group B returned on a separate day to undergo measurements of absolute GFR during an Ang-II infusion protocol identical to that during session 4. The sessions involving Ang-II overlapped with another experimental protocol that we reported on earlier. This overlap did not affect either dataset. All participants provided written informed consent and the study was approved by the institutional review board of the Academic Medical Center at the University of Amsterdam, The Netherlands.

**MRI data Acquisition**

All scans were performed on a 3T Ingenia MRI scanner (Philips Healthcare, Best, The Netherlands). The scanner had a maximum gradient strength of 45 mT/m and a peak slew rate of 200 mT/m/s. Data were acquired with a 16-channel phased-array anterior coil and a 10-channel phased-array posterior coil. Survey scans, including 3D Dixon, were used to locate the position of the kidneys.

We acquired DW-images with a single shot echo-planar imaging read-out with coronal slice orientation. Images were acquired continuously during free breathing at 16 different diffusion weightings of $b=0, 2, 4, 8, 12, 18, 24, 32, 40, 50, 75, 110, 200, 300, 450, 600$ s/mm$^2$. 

| 102 |
For \( b = 0 \), 75 and 600 mm\(^{-2}\)s, images were acquired at sixteen different gradient directions, 1 average per gradient direction. The other b-values were acquired at nine gradient directions. Further image parameters were: FOV=280\( \times \)224 mm\(^2\), resolution=3.5\( \times \)3.5 mm\(^2\), slice thickness=3.5 mm, slice gap=0.5 mm, 20 slices, TR/TE=2068/61 ms, BW=35 Hz/voxel in the phase encoding direction, parallel imaging factor (SENSE) of 2 and a spectral pre-saturation with inversion recovery (SPIR) pulse, as well as gradient reversal during slice selection, for fat saturation. Acquisition time for DW-MRI scans was 6 minutes and 6 seconds.

**Image processing and segmentation**

To overcome breathing motion in the acquired MRI data and align the kidneys in the acquired images, we used the following registration technique, as described previously for renal DWI\(^8,14\). In short, we assumed that respiratory motion predominantly occurred in the superior-inferior direction and that through-plane motion (anterior-posterior) was negligible. Therefore, alignment of the kidneys could be done slice-wise. Per slice, we produced the mean image of replicate images acquired at \( b = 0 \) s/mm\(^2\) (b\( \_ \)0-images, Fig. 1C). All b\( \_ \)0-images of that slice were then registered to this mean b\( \_ \)0-image and aligned accordingly. Registration
was done using an affine transformation based on mutual information, non-rigid 2D b-spline in Elastix toolbox (Version 4.7, University Medical Center Utrecht and contributors, Utrecht, The Netherlands). From these registered and now aligned images, a new motion corrected mean b0-image was created (Fig. 1E). Finally, all subsequent images corresponding to the slice were registered to this new motion corrected mean b0-image, using the aforementioned non-rigid 2D b-spline transformation.

In the motion corrected images, ROIs containing the kidney cortex and medulla were delineated in each slice using ITK-snap (Version 3.2.0, University of Pennsylvania, Philadelphia, PA and University of North Carolina, Chapel Hill, NC) (Fig. 1E). On average 15 ± 1.7 out of 20 slices contained the kidney and each segmented kidneys contained 4178 ± 717 voxels. All further analyses were performed using the DTITools toolbox for Mathematica (Mathematica 10.3, Wolfram Research Inc., Oxfordshire, United Kingdom). The mask was eroded to remove the outer voxels and to avoid voxels from outside the kidneys entering the ROI by residual displacements after registration. All DW scans were analyzed using this method.

Model and fitting
As the bi-exponential model described the data insufficiently (Fig. 1A), we used the following tri-exponential model that was fitted to each individual delineated voxel separately, before averaging the model parameters for the entire delineation:

\[ S(b) = S_0 \cdot (1 - f_i - f_f) \cdot -\exp[b \cdot D] + f_i \cdot -\exp[b \cdot D^*] + f_f \cdot -\exp[b \cdot D^{*}\!\!\!i] \].

[Equation 1]

Here, \( S(b) \) was the signal magnitude as a function of \( b \), \( S_0 \) the fitted signal magnitude at \( b=0 \) s/mm\(^2\), \( D \) the diffusion coefficient, and \( f_i \) and \( f_f \) the signal fractions corresponding to the intermediate pseudo-diffusion coefficients \( D^* \), and fast pseudo-diffusion coefficient \( D^{*}\!\!\!i \), respectively (see Fig. 1D for typical fraction maps). When delineations still contained voxels covering part of the renal calyces, this resulted in supra-normal \( f_i \) or \( f_f \) fractions. Therefore, all voxels with a \( f_i \) or \( f_f \) fraction >0.25 were excluded from analyses in all of the experiments. In addition, we defined the tissue fraction \( f_0 \) to be

\[ f_0 = 1 - f_i - f_f \].

[Equation 2]

which was calculated after the fit. Usually, when applying an IVIM model, the \( D^* \) parameter(s) are fixed to improve the robustness of the fit. Therefore, all analyses were performed in four-fold, as summarized in Table 1. In this model \( f_i \) and \( D^* \), represent the fraction of fast/bulk motion, \( f_f \), and \( D^{*}\!\!\!i \), represent a fraction of intermediate incoherent motion and \( f_0 \) and \( D \) represent classic tissue diffusion.
Kidney specific intravoxel incoherent motion analysis

Table 2 Different fit approaches

<table>
<thead>
<tr>
<th>Constraints</th>
<th>D (×10–3 mm²/s)</th>
<th>D* (×10–3 mm²/s)</th>
<th>D* (×10–3 mm²/s)</th>
<th>f, and f₁</th>
</tr>
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<tr>
<td>Free-D*s</td>
<td>Constrained</td>
<td>Constrained</td>
<td>Constrained</td>
<td></td>
</tr>
<tr>
<td>Fixed-D*s</td>
<td>Constrained</td>
<td>D*₁ = 9.7</td>
<td>D*₂ = 551</td>
<td></td>
</tr>
<tr>
<td>Fixed-D*₁</td>
<td>D*₁ = 9.7</td>
<td>Constrained</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fixed-D*₂</td>
<td>Constrained</td>
<td>D*₂ = 551</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fit parameters were either fixed to a value or constrained to a domain. The constraints are indicated in the second row, whereas the different fit approaches are shown in the subsequent rows.

IVIM model optimization

We tested the effect of fixing D*₁ and D*₂ on the actual changes in the D*₁ and D*₂ parameters. To this end we simulated data sets using Eq. 1 with known input parameters, derived from a free fit to all averaged baseline data (f*₁ = 0.16, f*₂ = 0.06, D*₁ = 1.9×10–3 mm²/s, D*₂ = 9.7×10–3 mm²/s and D*₃ = 551×10–3 mm²/s). We performed two in silico simulations; first we varied D*₁ from 0.5×D*₁⁻¹ to 2×D*₁ (in steps of 0.1), secondly, we varied D*₂ from 0.5×D*₂⁻¹ to 2×D*₂ (in steps of 0.1). We introduced random Rician noise to the clean data-sets with a signal-to-noise ratio (SNR) of 40 at b=0. The amount of noise was the same at all b-values. Consequently, the SNR decreased as the signal diminishes at increasing b-values. Subsequently, we fitted the IVIM model using the four methods explained above (Table 1): free-D*s, fixed-D*s, fixed-D*₁ and fixed-D*₂ fits. For each data set the simulation was repeated 1000 times while in each repetition, a random Rician noise was added to the clean data. After 1000 repetitions, the data with f₁ or f₂ larger than 0.25 were removed in order to mimic the in vivo situation. Then, the mean and quartiles of the remaining data were determined and plotted as a function of the induced changes in the D*₁’s.

Reproducibility

From the data of scan session 1, and scan sessions 2 and 3 respectively, intra- and inter-session variability for each f₁ and D-parameter were quantified using the within-subjects coefficients of variation (wCV) and visualized by Bland-Altman plots (GraphPad Prism 6, GraphPad Software, La Jolla, CA).

Angiotensin II intervention

Eight healthy young volunteers were subjected to three increasing doses of continuous intravenous Ang-II infusion at 0.3, 0.9 and 3.0 ng/kg/min, as described in detail previously. Ang-II is a potent vasoconstrictor of which the effects are most pronounced in the efferent arterioles running from the glomeruli. Therefore, Ang-II infusion results in an increased systemic blood pressure, decreased renal plasma flow (RPF) and increased filtration fraction.
Data simulations. The net effect is an unchanged (or even increased) glomerular filtration rate (GFR) at a low dose and a slight decrease at a higher dosage.\textsuperscript{12,20}

During baseline and each Ang-II dose, DW-MRI scans of the kidney and phase contrast MRI scans of the renal artery were acquired after an initial run-in period of at least 120 s after each Ang-II dose increase. Total scan time per dose Ang-II was approximately 10 minutes. From the phase contrast data, the RPF was calculated as we described previously.\textsuperscript{13} After the Ang-II MRI session, each subject returned on a separate day to undergo measurements of absolute GFR during an identical Ang-II infusion protocol. Absolute GFR was measured by the clearance of the constantly intravenously infused tracer $^{125}$I-Iothalamate (Glofil-125, Iso-Tex Diagnostics, Friendswood, TX).\textsuperscript{21} Ang-II induced a maximum RPF reduction from 660 ± 48 at baseline to 467 ± 36 mL/min/1.73m$^2$ and a GFR decrease from 121 ± 7.6 to 110 ± 6.6 mL/min/1.73m$^2$.\textsuperscript{13}

The effects of progressive renal blood flow reduction by Ang-II infusion on the signal fraction parameters were assessed by MANOVA for repeated measures using either the free-D*s or fixed-D*s fit methods. In case significance was reached according to Wilks’ $\Lambda$, then each of the $f$-parameters’ contribution to the model was subsequently assessed (SPSS Statistics 22, IBM, Chicago, IL).

Subsequently, correlations between the changes in the fraction parameters and the changes in RPF and GFR were assessed using single and multivariate linear regression analysis. To take the repeated measurements relations and the dependence of the $f$-parameters to one another into account, first, each individual subject’s Ang-II response was quantified by linear regression analysis. Then, the $f$-parameters’ slope coefficients were entered into multivariate linear regression analysis to assess the parameters’ relation to the RPF and GFR (SPSS Statistics 22, IBM, Chicago, IL).

For all statistical tests, a p-value <0.05 was considered significant.

| RESULTS |

Data simulations
In the free-D*s fit, changes in $D^*$, resulted in changes of the fitted $D^*$, $f$, and $f_i$ remained stable (Fig. 2A top row). Changes in $D^*$, however, did not result in changes of the fitted $D^*$, (Fig. 2A bottom row). In the fixed-D*s fit, changes in $D^*$, resulted in changes of $f$, and $f_i$. If $D^*$, decreased, $f$, decreased and $f_i$, remained stable. If $D^*$, increased, $f$, remained stable and $f_i$, decreased. (Fig. 2B top row). Changes in $D^*$, resulted in a very small inverse change of $f_i$ (Fig.}
As at these values of \( D^* \), almost instantaneous spin dephasing occurred between \( b=0 \) s/mm\(^2\) and \( b=2 \) s/mm\(^2\), changes in \( D^* \) had little effect on \( f_i \) or \( f_f \) in both the free-\( D^* \)'s and fixed-\( D^* \)'s fits.

The results of fixing either one of the \( D^* \)'s only, can be found in the supplementary materials (see Figure I, Supplementary materials 1, which demonstrates the model’s behavior in case either \( D^*_i \) or \( D^*_f \) was fixed). Those data show that fixing one of the \( D^* \)'s limits bias to one exponent only.

**Reproducibility**
Fixing \( D^* \)'s (Fig. 3 in blue) nor leaving them free (Fig. 3 in red) affected the intra-session repeated measurements. No offsets on the y-axes were observed. Using free-\( D^* \)'s resulted in the least inter- and intra-session variation in \( f \)-parameters, but introduced more variation in
Table 2 Intra- and inter-session wsCVs (%) for fixed- and free-D* models.

<table>
<thead>
<tr>
<th>Intra-session</th>
<th>$f_0$</th>
<th>$f_i$</th>
<th>$f_f$</th>
<th>$D$</th>
<th>$D^*_i$</th>
<th>$D^*_f$</th>
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<tr>
<td>Fixed-D*s</td>
<td>2.4</td>
<td>14.6</td>
<td>7.3</td>
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<td>NA</td>
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<td>0.7</td>
<td>4.0</td>
<td>8.0</td>
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<td>11.3</td>
<td>6.8</td>
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<table>
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<th>Inter-session</th>
<th>$f_0$</th>
<th>$f_i$</th>
<th>$f_f$</th>
<th>$D$</th>
<th>$D^*_i$</th>
<th>$D^*_f$</th>
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<tr>
<td>Fixed-D*s</td>
<td>2.0</td>
<td>10.4</td>
<td>18.8</td>
<td>1.1</td>
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<tr>
<td>Free-D*s</td>
<td>0.8</td>
<td>3.5</td>
<td>19.4</td>
<td>2.4</td>
<td>13.6</td>
<td>5.9</td>
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</table>

$D$ (Tab. 2). Fixing $D^*$ increased the wsCV of the $f_i$ and $f_f$ parameters both inter- and intra-session (Tab. 2). Fixing either of the $D^*$ individually, did not change reproducibility of the model compared to both the fixed-D* or the free-D* fit (Table 1, Supplementary materials 2, which contains wsCV values for intra- and inter-session variability of all parameters for each model configuration).

![Bland-Altman plots depicting inter-session variability of $f_0$, $f_i$, and $f_f$](image)

**Figure 3** Inter-session variability

Bland-Altman plots depicting inter-session variability of $f_0$ (top middle), $f_i$ (top right), $f_f$ (top left), $D$ (bottom left), $D^*_i$ (bottom middle), $D^*_f$ (bottom right), free-D* (red) and fixed-D* (blue). The corresponding wsCVs are shown in Table 2. Fixing $D^*$ (in blue) or not leaving them free (in red) affected the repeated measures data. There are no significant offsets from 0 on the y-axes.

**Angiotensin II intervention**

Figure 4 shows the IVIM parameters changes induced by Ang-II infusion. The direction of the response in the fraction parameters was the same for both fit methods, i.e. free-D* and fixed-D*. In the free-D* fit, $f_i$ decreased by $4.3 \pm 3.7\%$ (from $0.149 \pm 0.005$ to $0.142 \pm 0.003$) and $f_f$ increased by $28.0 \pm 12.6\%$ (from $0.058 \pm 0.006$ to $0.071 \pm 0.006$, Fig. 4A)
between baseline and maximum Ang-II dose. However, this response was not significant in multivariate analysis (F(3, 28) = 1.631, p = 0.205, Wilks’ Λ = 0.851, partial η² = 0.149).

With D*’s fixed, $f_i$ decreased by 14.0 ± 6.5% (from 0.138 ± 0.008 to 0.117 ± 0.008) and $f_f$ increased by 31.9 ± 12.5% (from 0.057 ± 0.006 to 0.072 ± 0.005). In contrast to the free fit, here the response of $f_i$ and $f_f$ to Ang-II was significant (F(3, 28) = 3.123, p = 0.042, Wilks’ Λ = 0.749, partial η² = 0.251). In this multivariate analysis, only the contribution of $f_f$ was significant (F(1, 31) = 9.600, p = 0.004), $f_i$ showed no significant contribution (F(1, 31) = 3.868, p = 0.059, Fig. 4B).

As we only observed a significant trend in fit parameters using the fixed-D*’s model, we selected this model to test for correlations to GFR and RPF. $f_i$ correlated to GFR (R = 0.39, p = 0.026, Fig. 5A) and there was an inverse correlation between $f_f$ and RPF (R = -0.70, p < 0.01, Fig. 5B).

**DISCUSSION**

In this study, we introduced reproducible method for IVIM analysis which allows studying the specific rheological properties of the kidneys. Expanding the traditional bi-exponential approach to IVIM analysis – accounting for one perfusion fraction and tissue diffusion – to incorporate a third exponent into the model, thereby accounting for blood perfusion, pre-urine flow, and tissue diffusion. This tri-exponential IVIM analysis was able to detect changes in renal perfusion during pharmacologically induced renal perfusion modulation. The response in the fraction of fast signal decay ($f_f$) correlated to RPF measurements and the
fraction of intermediate signal decay ($f_i$) to GFR, corroborating that the model differentiates between bulk perfusion and urine related flow patterns.

In an ideal kidney-specific tri-exponential IVIM model three separate signal fractions ($f$-values) for tissue, blood, and pre-urine associated particle motion would be determined. However, as will be discussed further, we find that the fast exponent ($f_f$ with $D^*$) most likely constitutes bulk motion in larger vessels, whereas capillary perfusion, as well as tubular pre-urine flow, are both contained in the intermediate exponent ($f_i$ with $D^*$).

The value of $D^*$, when fitted to the mean data ($551\times10^{-3} \text{ mm}^2/\text{s}$), corresponds to almost instantaneous signal decay. As a consequence, this high value of $D^*$, most likely indicates bulk motion, due to instant dephasing of spins in blood in larger vessels as a result of the local flow profile. As for the $D^*$, value; this is consistent with both capillary blood and tubular pre-urine flow velocity. The value of $D$ is well in the range of tissue diffusion in other organs. Thus, our data suggest that we indeed are able to differentiate between three distinct fractions, i.e.: a diffusion fraction ($f_d$) related to stromal kidney tissue; an intermediate bulk motion fraction ($f_i$) related to capillary perfusion and pre-urine flow; and a fraction of fast bulk motion ($f_f$) related to blood flow in larger vessels.

Regarding the value of $D^*$, this signal decays by a factor 3 for every increase of b-value by 2 s/mm$^2$. Considering an initial signal fraction of $f_i = 0.06$, the signal will have decayed to 6%/3 = 2.0% and 6%/3/3 = 0.7% of the signal at the first two b-values acquired. Given the SNR of our measurements, fitting $D^*$ cannot be reliable, as was reflected in our simulations. Also, for this reason, $D^*$ was restricted to <1000$\times10^{-3}$ mm$^2$/s. Generally, when renal IVIM analysis is performed, only a limited number of b-values below 25 s/mm$^2$ are acquired.
As a consequence, it becomes more challenging to distinguish between the instantaneous dephasing, as described by the high \( D^* \) in this work, and the perfusion/urine effect of \( D^* \). For example, for a lowest non-zero b-value of 25 s/mm\(^2\), the IVIM model fit is only sensitive for \( D^* \)-values \(<65\times10^{-3}\) mm\(^2\)/s, as only 20% of the original signal from this compartment would remain at this value. This is also a reason to use the fixed-\( D^* \)s model.

Previous IVIM applications in the kidney have used varying approaches to limit or constrain the bi-exponential model's parameters.\(^{7,9,23-25}\) Reducing the number of fit parameters by fixing \( D^* \) was used previously to increase the stability of IVIM fits (albeit at the cost of losing information on \( D^* \)).\(^{10}\) By incorporating a third exponent, the number of fit parameters increases from 4 to 6. In this case, it could be particularly useful to limit the number of variables. In contrast to the bi-exponential fit, our simulations and repeated measures both showed that for the tri-exponential fit, fixing the \( D^* \)s in the kidneys did not improve the repeatability.

The simulations show that the fixed-\( D^* \)s fit potentially introduces a systematical error to the perfusion parameters. However, when comparing the different fit methods in the Ang-II intervention data, the fixed-\( D^* \)s fit improved the model's sensitivity to detect perfusion changes and hence was preferred. We speculate that in the case of Ang-II infusion, both the \( f \)- and \( D^* \)-parameters are affected. In the free-\( D^* \)s fit, changes of both these parameters are accurately described by the model resulting in changes of both \( D^* \)- and \( f \)-parameters. However, these changes are small and outside the precision of the model. For the fixed-\( D^* \)s fit, physical changes in \( D^* \)s and \( f \) are combined, and both are reflected in the \( f \)-parameters, thereby strengthening the response of the \( f \)-parameters. This approach results in a trend that is detectable within the parameters' precision. Therefore, we chose to fix both \( D^* \)s and only correlate those results with the GFR and RPF measurements.

We correlated the intermediate diffusion signal fraction (\( f_i \)) to the GFR and the fraction of fast bulk motion (\( f_b \)) to the RPF. At first sight, the inverse relation between \( f \) and RPF is surprising, since renal blood flow decreases and thus the fraction of fast bulk motion would decrease as well. However, we can directly relate these results to the effects of Ang-II on the kidney's perfusion and filter function. Ang-II predominantly acts as a vasoconstrictor in the efferent arterioles running from the glomeruli.\(^{20}\) This post-glomerular vasoconstriction results in blood pooling in the supplying blood vessels, thereby increasing blood volume of these larger vessels i.e. the volume that contributes to the fraction of fast bulk motion (\( f_i \)). This increase in \( f_i \), in turn, could suppress the urine volume ratio leading to the decrease in \( f \).

Our study has some methodological limitations that merit discussion and should be considered in future technique developments. First, our exploration was limited by the current voxel size (3.5x3.5x3.5 mm), that did not allow reliable differentiation between kidney cortex
and medulla although there are structural differences. Secondly, we did not apply strategies to decrease the influence of bulk motion on the other fit variables at acquisition. This may have limited the differentiation between blood and urine associated signal fractions. The introduction of motion compensating gradients may prevent the instantaneous dephasing in the large vessels and improve the renal IVIM model. Secondly, we did not apply strategies to decrease the influence of bulk motion on the other fit variables at acquisition. This may have limited the differentiation between blood and urine associated signal fractions. The introduction of motion compensating gradients may prevent the instantaneous dephasing in the large vessels and improve the renal IVIM model. Lastly, in order to reduce scan time we choose to image during free breathing and register the images during post-processing rather than applying respiratory gating or triggering. Although, biologic contrast and retro-peritoneal anatomy of the kidneys allow for very effective image registration, there might be some motion induced signal variation in the data.

CONCLUSIONS

We further developed a reliable and reproducible kidney-specific method for IVIM analysis using a tri-exponential model. Although fixing both D*'s may introduce bias to the perfusion fractions, it improves the sensitivity of the model to changes in renal perfusion at the same time. Furthermore, our results indicate that a tri-exponential IVIM model can track changes induced by modulation of renal perfusion. Its further development might provide new opportunities for a non-invasive, spatially differentiated assessment of kidney perfusion and filter function in kidney disease.

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LIST OF SUPPLEMENTARY MATERIALS

Supplementary material 1
Supplementary material 2
Supplementary materials can be found in the appendices of this thesis.
REFERENCES


