MR IMAGING BIOMARKERS FOR BENIGN PROSTATIC HYPERPLASIA PHARMACOTHERAPY

DIS SUR TATION

Presented in Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy in the Graduate School of The Ohio State University

By

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* * * * *

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ABSTRACT

Benign prostatic hyperplasia (BPH) is a highly prevalent disease in older men and occurs in more than 50% of men aged 60 to 70 years. BPH results in prostate enlargement with bladder outflow obstruction. Treatment with a 5α-reductase inhibitor such as finasteride induces apoptosis in epithelial cells and leads to the reduction of prostate volume. However, pharmacologic treatment is not uniformly effective in shrinking the prostate and in relieving symptoms, so the ability to predict how each patient will benefit best from varying pharmacotherapy is a question of great medical and economic importance.

Finasteride is also used as a prophylaxis of BPH-associated hematuria and to reduce blood loss at surgical resection of the prostate. The important questions to be addressed include what is the optimum dose and how long should the patients be treated. An effective non-invasive tool may be helpful to solve these questions by monitoring the changes in prostatic blood flow.

Twenty-four male beagles with benign prostatic hyperplasia were enrolled in a drug trial and imaged at five time points by magnetic resonance imaging (MRI). The capabilities of different MRI-based methodologies for measuring prostate volume were evaluated from anatomical MR images. The possibility of using pharmacokinetic parameters as a predictor of MRI prostate volume changes were evaluated and the use
of DCE-MRI as a biologic marker of in-vivo changes in microcirculation in prostatic suburethral region was assessed.

The segmented MRI prostate volume significantly correlated with post necropsy volume. The changes in prostate volume at the end of the treatment exhibited a significant linear correlation to the initial parenchymal Maximum Enhancement Ratio (MER) \((p < 0.02)\) in the finasteride group. After completion of the therapeutic regimen, \(T_{max}\) on prostatic suburethral area was significantly longer in the finasteride group compared to controls \((p < 0.01)\), and the pharmacokinetic parameters amplitude \(A\) and exchange rate constant \(k_{ep}\) decreased 39% and 34% respectively in the finasteride group at the end of the treatment.

In conclusion, MRI of prostate can supply important in-vivo biomarkers, such as organ volume and pharmacokinetic parameters, in the development of BPH pharmacotherapies such as 5α-reductase inhibitors.
This is dedicated to the ones I love most: my parents and my wife Tanping
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CHAPTER 1

INTRODUCTION

1.1 Background

1.1.1 Benign Prostatic Hyperplasia (BPH) and Symptoms

Diseases of the prostate have a profound impact on public health. Benign Prostatic Hyperplasia (BPH) has a high prevalence among older men [48], BPH occurs in more than 50% of men aged 60 to 70 years. BPH is a hyperplastic process involving the stromal and epithelial tissues of the prostate [60], which is characterized by progressive enlargement of the prostate gland often resulting in symptoms and bladder outflow obstruction [7]. Patients with BPH present with irritative and obstructive lower urinary track symptoms – urgency, frequency, nocturia, feeling of insufficient bladder emptying and weak or intermittent flow. BPH has higher risk of complications such as acute urinary retention and can reduce quality of life. Furthermore, BPH may be associated with sexual dysfunction [48].

1.1.2 BPH Treatment

Treatment options of BPH include pharmacotherapy, surgical management, and minimally invasive treatment, etc.
Pharmacotherapy includes 5α-reductase inhibitors, α1 blockers, etc. α1-blockers such as alfuzosin can relax prostatic smooth muscle and release the symptoms. Treatment with a 5α-reductase inhibitor such as finasteride induces apoptosis in epithelial cells and leads to the reduction of prostatic volume and the reversal of the BPH process [8, 2]. However, pharmacologic treatment is not uniformly effective in shrinking the prostate and in relieving symptoms, so the ability to predict how each patient will benefit best from varying pharmacotherapy is a question of great medical and economic importance [49, 26].

Surgical treatment is usually indicated for patients who have complications of BPH and who fail to respond to pharmacological treatment. Prostatectomy includes transurethral resection of the prostate (TURP), transurethral incision of the prostate (TUIP), and open prostatectomy. About 95% of prostatectomies are still carried out by TURP [24]. The outcomes of TURP, in terms of flow rate and symptom reduction, are usually good, while the complications of TURP include BPH-associated hematuria, bleeding and clot retention [50]. Any improvements in reducing these complications would be highly beneficial for patients. Minimally invasive treatments are used for patient with moderate or severe symptoms. The treatments include, e.g. laser ablation, transurethral microwave thermotherapy, and transurethral needle ablation.

1.1.3 BPH-related Hematuria and Prostate-Bleeding

Hematuria is the presence of red blood cells in the urine. Finasteride, a 5α-reductase inhibitor introduced as drug therapy for BPH, is also used as a prophylaxis of BPH-associated hematuria and to reduce blood loss at surgical resection of the
prostate [13, 31]. In 1993, Marshall and Narayan postulated that angiogenesis is critical in BPH and androgen deprivation leads to the suppression of angiogenesis [40]. The first reported use of finasteride to control hematuria associated with BPH was in 1995 [54]. The ability of pretreatment with finasteride to reduce perioperative bleeding at TURP was reported as early as 2000 [27]. One proposed underlying mechanism is that finasteride blocks the conversion of testosterone to dihydrotestosterone, decreasing the expression of vascular endothelial growth factor (VEGF) and inhibiting angiogenesis, which decreases microvessel density (MVD) in prostatic suburethral tissue [29, 52]. By this mechanism, finasteride significantly reduces blood loss during surgical treatments [13], and suppresses hematuria secondary to BPH [31, 21]. The important questions to be addressed about finasteride treatment include, what is the optimum dose and how long should the patients be treated [21, 17]. An effective non-invasive tool may be helpful to solve these questions by monitoring the changes in prostatic blood flow.

1.1.4 Anatomic MR Imaging of BPH

In addition to qualitative morphological imaging for diagnostic purposes, quantitative determination of the prostate volume is also important in the diagnosis and treatment of BPH [4, 15, 56]. Prostate volume is especially important for selection of the most appropriate treatment in patients requiring intervention [25]. Moreover, objective and early assessment of volume reduction is essential for evaluating continuous pharmacological therapies such as anti-androgens and other medical agents [64, 32].

Because of the organ’s soft tissue contrast in magnetic resonance imaging (MRI), MRI data sets can be used for accurate delineation of the prostate [62, 55]. For
volume assessment in MRI, the prostate outline has been traced either manually or with the assistance of computer programs on a slice-by-slice basis by planimetry in axial images [12, 46, 47]. Some diameter-based methods have been used and compared to slice-by-slice segmentation methods. For example, the prolate ellipsoidal approximation was taken by measuring the longest transverse, anterior-posterior, and superior-inferior diameters in the axial and sagittal MR images [44, 6]. Another ellipsoidal volume approximation has been obtained using the prostate’s width and height from the largest prostate contour on MRI and the prostate length from the number of slices on which the prostate was depicted and the slice-to-slice distance [45].

1.1.5 Functional MR Imaging of BPH

Dynamic contrast-enhanced MRI (DCE-MRI) by intravenous injection of extracellular Gd-chelate contrast agents provides an exciting opportunity to non-invasively study the microcirculation and microenvironment of tumors and abnormal tissues at high spatial and temporal resolution and without ionizing radiation [51, 34, 72, 11, 53]. The use of pharmacokinetic parameters to characterize the microenvironment in prostatic tissues may lead to improving the reliability of diagnosis of BPH and assessing therapeutic responses as well as predicting the outcome of pharmacotherapy [28]. The pathway of small molecular weight contrast agent in the region of interest can be detected by the enhanced signal intensity in T1-weighted MR images, which usually has a linear relationship to the concentration of the contrast agent in certain range. Signal intensity parameters and pharmacokinetic parameters are used to analyze the contrast agent concentration (signal intensity) and resultant changes with time and to quantify and visualize microvascular characteristics such as microvessel density,
vascular permeability and VEGF expression [51]. The quantitative potential of the technique has led it to be a tool for monitoring response to treatment.
CHAPTER 2

MATERIALS AND METHODS

2.1 Animals and Experimental Model

The study was prospectively designed within an interdisciplinary team and approved by the local animal care committee. Twenty-four male beagle dogs (mean age ± SD: 4.4 ± 0.9 years, range 3 to 6 years) with an initially palpated prostate diameter larger than 2 cm were selected for this trial. The subjects were divided into four therapeutic groups with six subjects in each group: a conventional 5α-reductase inhibitor (Finasteride, Merck & Co., Whitehouse Station, NJ) group, two groups with different doses of an experimental BPH drug (SCH 488900, Schering-Plough Co., Kenilworth, NJ) (the higher dose group was defined as dose A group; the lower dose group was defined as dose B group), and a control group that received placebo treatment. The duration of the treatment was 12 weeks.

The subjects were imaged five times by MRI: Study #1 (ST1, Baseline #1) was carried out at 3 weeks prior to treatment (weeks -3), and study #2 (ST2, Baseline #2) immediately prior to initiation of treatment (week 0). Study #3 (ST3, week 4), study #4 (ST4, week 8), and study #5 (ST5, week 12) were done after the beginning
Figure 2.1: Two baseline MR scans and three during-treatment scans were implemented during this study.

of treatment (Figure 2.1). This resulted in a total number of 120 volumetric and DCE-MRI prostate image data sets.

Two days after study #5, the dogs were euthanized to extract the prostate. After removal of as much of the surrounding periprostatic fat and connective tissue as possible, prostate volumes were then measured by the water-displacement method.

2.2 MR Imaging

All MRI examinations were performed on a 1.5T clinical MRI system (Twinspeed, GE, Milwaukee, WI; Figure 2.2) using the standard head coil with the subjects imaged in the prone position (Figure 2.3). The beagles were anesthetized for the purpose of restraint and constraint during all MRI examinations. Anesthesia was induced with Diazepam (1 mg/kg) and Xylazine (1 mg/kg), followed by maintenance of Isoflurane inhalation (1-3%).

After routine localization images, axial and coronal T2-weighted fast spin echo images (TR/TE/\(\alpha\) = 2000 ms/105 ms/90\(^{\circ}\); field of view = 140 \(\times\) 140 mm\(^2\), matrix = 256 \(\times\) 256 with in plane resolution 0.55 \(\times\) 0.55 mm\(^2\); NEX = 1; 25 slices; 2.0-mm slice thickness, contiguous slices) and axial T1-weighted spin echo images (TR/TE/\(\alpha\)
Figure 2.2: The mobile clinical 1.5 T scanner with beagle inside for MR imaging.

Figure 2.3: The beagle was placed in a clinical head coil in the prone position. The right figure is the apparatus for isoflurane inhalation.
= 500 ms/20 ms/90°; field of view = 140 × 140 mm², matrix = 256 × 256 with in plane resolution 0.55 × 0.55 mm²; NEX = 0.5; 25 slices; 2.0-mm slice thickness, contiguous slices) were acquired completely covering the prostate. The acquisition time of the axial T2-weighted images, coronal T2-weighted images, and axial T1-weighted images was 3 minutes 49 seconds, 3 minutes 25 seconds, and 4 minutes 32 seconds respectively.

DCE-MRI was performed using a 3D spoiled gradient echo (3D-SPGR) imaging sequence (TR/TE/α = 7.5 ms/2.6 ms/25°, field of view = 140 × 140 mm², matrix = 256 × 256, in-plane resolution = 0.55 × 0.55 mm²; NEX = 0.5; 2.0-mm slice thickness, contiguous slices; 26 slices, Acquisition time per volume: 24 s, 32 time points). The extracellular contrast agent Gadoteridol (ProhanceTM, Bracco Diagnostic Inc, Princeton, NJ, 0.2 mmol/kg bodyweight) was intravenously injected at a rate of 0.2 ml/s after 3 time points using a power injector (Spectris, MedRad, Indianola, PA) followed by a 15 ml flush of saline solution injected at a rate of 0.2 ml/s).

2.3 Image Analysis

2.3.1 Prostate Volume Evaluation

In order to determine the precision of in-vivo prostate volume measurements, we compared the volume obtained by MRI-based semi-automated segmentation to the post-necropsy volume as determined by the water-displacement method. Diameter-based models for estimating prostate volume were constructed based on specific diameter measurement approaches obtained from single slices. The models were applied to different therapy groups in order to verify whether they were sensitive enough for monitoring changes in prostate volume during ongoing therapy.
2.3.2 DCE-MRI Analysis Methodology

DCE-MRI is highly efficient to monitor changes induced with medical treatments, like finasteride [28], and minimally invasive therapies, such as laser ablation of the prostate [5]. The kinetics of the intravenously-injected contrast agent in prostate tissue can be depicted by quantifying the time-signal intensity curves in dynamic MRI data. The quantification of the time-signal intensity curves can be carried out through a pharmacokinetic model and the generated pharmacokinetic parameters can be used to characterize the microcirculation and microenvironment of the prostate. Several different models are used for analyzing DCE-MRI data [70, 71, 66, 67]. It is important to select the appropriate pharmacokinetic model to characterize the time-signal intensity curves in highly vascularized prostate. The purpose of this study was to systematically investigate the goodness-of-fit and the reproducibility of the pharmacokinetic models on fitting the parenchymal, periurethral and suburethral regions in beagle prostates. The goodness-of-fit and the reproducibility of these models were examined in the two baselines prior to the treatment.

2.3.3 Pharmacokinetic Parameters and Prostate Volume

In this study, the response to finasteride was investigated in older beagles with spontaneously occurring BPH. Conventional MRI for volume measurement and DCE-MRI for microcirculation assessment in the prostate were implemented with two baseline and three follow-up examinations. The possibility of using baseline pharmacokinetic parameters as a predictor of therapy-induced prostate volume reduction was also investigated.
2.3.4 Pharmacokinetic Parameters and Prostate Blood Flow

In this study we investigated dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) of the prostate and assessed the potential of the pharmacokinetic parameters as biomarkers to evaluate microvascular changes in the prostate. The use of DCE-MRI has become increasingly widespread for quantifying and visualizing microvascular characteristics such as microvessel density and vascular permeability. Its correlation to VEGF expression has also been recognized [37]. The contrast agents in DCE-MRI, such as the Gd-chelate complex, are small contrasting molecules with properties that increase the signal intensity in T1-weighted MR images [33]. The agent is intravenously injected, follows the pathway of blood circulation, enters into extravascular space (wash-in phase), and then diffuses back into the vasculature (wash-out phase), thereby acting as a probe to visualize microcirculatory properties [34]. By drawing a region of interest on certain tissues in dynamic MR images, one can observe and measure the signal intensity of the baseline images prior to arrival of the contrast agent, the signal intensity increase during the wash-in phase of the contrast agent, and the signal intensity decrease during the wash-out phase. The specific MR imaging sequences enable the quantitative calculation of the relative contrast agent concentration (uptake) and its changes over time (pharmacokinetics). This can be quantified by modeling tracer kinetics in a two-compartment model, that calculates the pharmacokinetic parameters to describe the time-concentration pattern [67]. The pharmacokinetic parameters such as exchange rate constant were shown to be significantly correlated with microvessel density in prostate tumors [59].

Using DCE-MRI to detect the finasteride-induced microvessel changes, the prostatic suburethral regions were investigated in an experimental dog prostate model.
Pharmacokinetic parameters as measurements of the DCE-MRI data were compared between the finasteride-treated group and the control group.
CHAPTER 3

PROSTATE VOLUME ASSESSMENT

3.1 Introduction

To evaluate the capabilities of different magnetic resonance imaging (MRI)-based methodologies for measuring prostate volume, twenty-four male beagles with benign prostatic hyperplasia were enrolled in a drug trial and imaged at five time points. A total of 120 MRI datasets of prostate (24 beagles × 5 time points) were acquired and used to determine the prostate volume by MRI-based semi-automated segmentation. For planimetric assessment, eight diameter locations were determined in the axial and coronal plane of the MRI slice with maximum extension of the prostate. Thirteen calculation models based on these diameters were determined by regression to the MRI segmented volume and evaluated during treatment. The segmented MRI prostate volume significantly correlated with post necropsy volume. The best diameter-based model also worked very well for monitoring prostate volume of dogs under treatment. MRI-based segmentation is highly accurate in assessing prostate volume. Diameter-based measurements are closely correlated to the segmented prostate volume and are feasible to monitor therapy.
3.2 Materials and Methods

3.2.1 Image Analysis

All post-processing of the volumetric datasets, i.e. volumetric and planar measurements of diameters, was done using the MIPAV (Medical Image Processing, Analysis, and Visualization) software package [41].

For volume determination by segmentation of the prostate in MRI data sets, its contours were delineated using a semi-automated segmentation method. This method relies on the advantages of T1-weighted and T2-weighted images. T1-weighted MRI images have a relative homogeneous signal within the prostate but are burdened with an iso-intense appearance between prostate and rectum and thus imprecise delineation of the border between them. T2-weighted images provide clear borders between prostate and surrounding tissues [42] but the signal intensity within the prostate is inhomogeneous as it reflects the underlying characteristics of the glandular tissue. It is therefore difficult to perform fully automated segmentation of the prostate in T2-weighted images. Applying an automated algorithm to T1-weighted images for automation and border adjustment for separation of prostate from rectum in T2-weighted images seems to be an acceptable solution compared to manual slice-by-slice segmentation of the prostate. In the first step, a circle was manually drawn inside the prostate as an initial 'estimation' of the prostate boundary in each T1-weighted axial slice containing the prostate. This estimation need not be precise, but it should indicate the general location and shape of the structure of the prostate. These circles were automatically evolved to the border of the prostate by using a 2-Dimensional boundary evolve algorithm, in which MIPAV applied a gradient magnitude filter to determine the structure’s boundary [41]. After copying the evolved contour to the
axial T2-weighted MR data set, minor border adjustment and separation of prostate from rectum were made by a trained and experienced investigator. All prostate contours were verified independently by two reviewers. The prostate volume was defined as the volume of all pixels inside the contours covering the whole prostate. The resulting volumes of the last MRI study (Study #5, n = 24) were compared to the prostate volumes obtained by the water-displacement method.

The planar prostate diameter measurements, which comprised the input data for model estimation, were carried out as follows: Axial and coronal T2-weighted images were examined for the slice with the largest cross-sectional extension of the prostate. Four diameters were drawn in the midaxial section (Figure 3.1A): (1) the longest left-to-right diameter in axial image (A0), (2) anterior-posterior (AP) diameter in the right lobe (A1), (3) AP diameter in the midline (A2), (4) AP diameter in the left lobe (A3); Four diameters were drawn in the midcoronal section (Figure 3.1B): (5) the longest left-to-right diameter (C0), (6) superior-inferior (SI) diameter in the right lobe (C1), (7) SI diameter in the midline (C2), (8) SI diameter in the left lobe (C3).

3.2.2 Model Definitions and Evaluations

In order to find the best correlation between prostate volumes determined by segmentation and these estimated based on diameter measurements, three set of models were investigated: the 1st set is based on a single diameter, the 2nd set is based on diameters in only one direction (axial or coronal plane), and the 3rd set uses diameters in both axial and coronal directions. This resulted in a total of 13 models for volume estimation of the prostate based on linear cross-section measurements. The
Figure 3.1: T2-weighted MR images at 1.5T (TR/TE = 2000/105 ms, 256 × 256 matrix and 0.55 × 0.55 mm²) with maximum prostate extension in axial and coronal directions. (A) Four diameters were defined in the axial T2-weighted images: A0 was the longest transverse dimension in the axial images; A1 was the anterior-posterior diameter in the right lobe; A2 was the anterior-posterior diameter in the midline; A3 was the anterior-posterior diameter in the left lobe. (B) Four diameters were drawn in the coronal T2-weighted images: C0 was the longest transverse dimension in the coronal images; C1 was the superior-inferior diameter in the right lobe; C2 was the superior-inferior diameter in the midline; C3 was the superior-inferior diameter in the left lobe.
baseline studies (Study # 1 and 2; 48 prostates in total) were used as a training group to determine the model parameters.

The 1st set consisting of eight models was based on single diameter: A0-Cubic, A1-Cubic, A2-Cubic, A3-Cubic, C0-Cubic, C1-Cubic, C2-Cubic and C3-cubic model. The models were defined by $V = \alpha \cdot \text{diameter}^3 + \beta$ with $V$ as the model-estimated volume. The parameter $\alpha$ (the slope) and $\beta$ (the intercept) were obtained by regression of the cubic of the specific diameter to the segmented prostate volumes in the training group.

The 2nd set (two models) was obtained by using all four diameters either of the axial or of the coronal images: The Axial-Area model and the Coronal-Area model. The “Axial-Area” and “Coronal-Area” were defined as the average of the three parallel diameters within a plane multiplied by the perpendicular diameter of the same plane. The two models were derived by introducing parameters $\alpha$ and $\beta$ through regression of “Axial-Area” or “Coronal-Area” to the segmented prostate volumes in the training group: Axial-Area model:

$$V = \alpha \cdot \left(40 \cdot \frac{A1 + A2 + A3}{3}\right) + \beta, \quad (3.1)$$

Coronal-Area model:

$$V = \alpha \cdot \left(C0 \cdot \frac{C1 + C2 + C3}{3}\right) + \beta. \quad (3.2)$$

The 3rd set (three models) was based on both axial and coronal diameters: The Cube model, Two-Ellipsoid model, and Box model, where “Cube” means a cube with side length equal to the average of all eight diameters, “Two-Ellipsoid” means a geometric object composed of two ellipsoids with the axes as the diameters in the right and left lobe of the prostates, and “Box” means a box with sides given by the average
of transverse diameters, the average of the AP diameters, and the average of the SI diameters respectively. The definitions of these models are as follows: Cube Model:

$$V = \alpha \cdot \left( \frac{A_0 + A_1 + A_2 + A_3 + C_0 + C_1 + C_2 + C_3}{8} \right)^3 + \beta,$$  

Two-Ellipsoid model:

$$V = \alpha \cdot \frac{\pi}{6} \cdot \frac{A_0 + C_0}{4} (A_1 \cdot C_1 + A_3 \cdot C_3) + \beta,$$  

Box model:

$$V = \alpha \cdot \frac{A_0 + C_0}{2} \cdot \frac{A_1 + A_2 + A_3}{3} \cdot \frac{C_1 + C_2 + C_3}{3} + \beta,$$  

The 3rd set of models were evaluated in the studies during treatment (Study #3, 4, 5) for the four treatment groups: the finasteride group (3 x 6 prostates), the dose A group (3 x 6 prostates), the dose B group (3 x 6 prostates), and the control group (3 x 6 prostates). The relative error volume was defined as the subtraction of the model estimated prostate volume from the segmented prostate volume divided by the segmented volume. The volume prediction error was calculated as the average of the absolute value of the relative error volumes for all subjects within a group. These values obtained from the four groups were used to check the validity and efficiency of these models for monitoring therapies.

3.3 Results

The average of the prostate volumes obtained by the water-displacement method (24 prostates) was 11 cm$^3$ with a SD of 5 cm$^3$ (range 6 to 25 cm$^3$) and the average of the segmented prostate volume of the last exam (Study # 5) was 13 cm$^3$ with a SD of 6 cm$^3$ (range 5 to 26 cm$^3$). The segmented prostate volumes (Study # 5,
Figure 3.2: Segmented MRI volumes of the prostate versus the volumes as obtained by water-displacement after necropsy. The segmented prostate volumes (mean ± SD: 13 ± 6 cm$^3$) were 9% larger than volumes obtained after necropsy (mean ± SD: 11 ± 5 cm$^3$). The correlation coefficient was 0.98 ($p < 0.05$).

24 prostates) correlated significantly to the prostate volumes obtained by the water-displacement method (correlation coefficient $r = 0.98$, $p < 0.05$, Figure 3.2). The segmented volumes were on the average overestimating the post-necropsy volumes by 9%.

The results of prostate volumes as obtained by segmentation of MRI data sets prior to and during treatment are shown in Table 3.1. The three trial groups experienced prostate volume reduction during therapy. At the last study (Study # 5), the relative
Table 3.1: Segmented prostate volumes (cm$^3$) by different trial groups. The dose A and B are the two different experimental BPH drug groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>Control</th>
<th>Finasteride</th>
<th>Dose A</th>
<th>Dose B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study #1</td>
<td>14.2 ± 6.2</td>
<td>13.7 ± 5.4</td>
<td>16.5 ± 3.8</td>
<td>15.5 ± 3.8</td>
</tr>
<tr>
<td>Study #2</td>
<td>14.7 ± 6.8</td>
<td>13.7 ± 5.3</td>
<td>17.4 ± 3.7</td>
<td>15.8 ± 2.9</td>
</tr>
<tr>
<td>Study #3</td>
<td>15.4 ± 6.0</td>
<td>8.9 ± 4.4</td>
<td>14.8 ± 4.1</td>
<td>10.3 ± 3.2</td>
</tr>
<tr>
<td>Study #4</td>
<td>14.6 ± 6.0</td>
<td>8.4 ± 4.2</td>
<td>13.0 ± 4.7</td>
<td>10.8 ± 3.4</td>
</tr>
<tr>
<td>Study #5</td>
<td>14.2 ± 6.4</td>
<td>7.2 ± 4.5</td>
<td>12.6 ± 5.5</td>
<td>10.7 ± 4.6</td>
</tr>
<tr>
<td>Post Necropsy</td>
<td>12.2 ± 6.3</td>
<td>7.2 ± 4.0</td>
<td>10.6 ± 4.1</td>
<td>9.2 ± 3.4</td>
</tr>
</tbody>
</table>

Volume reduction was 47% for the finasteride group, 27% for the dose A group, and 33% for the dose B group compared to the median prostate volume in the second baseline (Study # 2).

Using the pre-treatment MRI data sets, the regression parameters for the models were derived (Table 3.2). The 1st set of models based on a single diameter gave low correlation coefficients with a broad range (0.25-0.87). The 2nd set of models based on four diameters of axial direction or coronal direction provided good correlation coefficients (0.81-0.85). The 3rd set of models using diameters of both axial and coronal directions gave the highest correlation coefficient (0.95-0.96).

The 3rd set of models was applied to the prostates during therapy to check their validity among different drug trial groups. The prostate volume prediction results are shown in Table 3.3. For the Cube model, the volume prediction error was 7% for the control group (including subjects in all three during treatment studies), 7% for the finasteride group, 6% for the dose A group, and 7% for the dose B group. For the Two-Ellipsoid model, the volume prediction error was 7% for the control group, 10%
<table>
<thead>
<tr>
<th>Model Name</th>
<th>Slope $\alpha$</th>
<th>Intercept $\beta (cm^3)$</th>
<th>Correlation coefficient $r$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A0-Cubic</td>
<td>0.4</td>
<td>1.0</td>
<td>0.87</td>
</tr>
<tr>
<td>A1-Cubic</td>
<td>0.4</td>
<td>10.1</td>
<td>0.78</td>
</tr>
<tr>
<td>A2-Cubic</td>
<td>0.4</td>
<td>11.5</td>
<td>0.25</td>
</tr>
<tr>
<td>A3-Cubic</td>
<td>0.3</td>
<td>10.5</td>
<td>0.63</td>
</tr>
<tr>
<td>C0-Cubic</td>
<td>0.4</td>
<td>3.3</td>
<td>0.80</td>
</tr>
<tr>
<td>C1-Cubic</td>
<td>0.4</td>
<td>9.6</td>
<td>0.74</td>
</tr>
<tr>
<td>C2-Cubic</td>
<td>0.4</td>
<td>14.0</td>
<td>0.37</td>
</tr>
<tr>
<td>C3-cubic</td>
<td>0.6</td>
<td>7.9</td>
<td>0.80</td>
</tr>
<tr>
<td>Axial-Area</td>
<td>2.3</td>
<td>-2.4</td>
<td>0.85</td>
</tr>
<tr>
<td>Coronal-Area</td>
<td>2.2</td>
<td>0</td>
<td>0.81</td>
</tr>
<tr>
<td>Cube</td>
<td>0.8</td>
<td>2.2</td>
<td>0.95</td>
</tr>
<tr>
<td>Two-Ellipsoid</td>
<td>1.1</td>
<td>3.4</td>
<td>0.96</td>
</tr>
<tr>
<td>Box</td>
<td>0.7</td>
<td>2.2</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Table 3.2: Correlation and regression analysis for the models ($n = 48$). All p-values are less than 0.05. Correlation is significant at the 0.05 level (2-tailed).

for the finasteride group, 7% for the dose A group, and 6% for the dose B group. For the Box model, the volume prediction error was 7% for the control group, 8% for the finasteride group, 6% for the dose A group, and 7% for the dose B group.

3.4 Discussions

Volumetric assessment of the prostate is important in objectively determining changes during therapy for BPH. Sufficient validation of volumetric methods remains a common clinical challenge. We embarked upon this study to assess volumetric response to pharmacotherapy in beagles with BPH as an approach for objective validation before using this methodology in clinical trials or patient care. An advantage of using this animal model included the opportunity of directly comparing prostate
| Prostate volume estimation: median ± standard deviation (volume prediction error) |
|-----------------------------------------------|-----------------|-----------------|-----------------|
| Model                                           | Group           | Study # 3         | Study # 4         | Study #5         |
|-----------------------------------------------|-----------------|-----------------|-----------------|
| Cube Model                                     | Control         | 1% ± 5% (3%)     | 4% ± 6% (6%)     | -11% ± 10% (12%)|
| Finasteride                                    | 3% ± 10% (9%)   | -1% ± 5% (4%)    | -8% ± 4% (9%)    |
| Dose A                                         | 1% ± 6% (4%)    | 0% ± 9% (6%)     | -4% ± 7% (7%)    |
| Dose B                                         | 3% ± 11% (9%)   | 2% ± 6% (5%)     | -6% ± 6% (6%)    |
| Two-Ellipsoid Model                            | Control         | 6% ± 5% (6%)     | 7% ± 7% (8%)     | 0% ± 8% (6%)    |
| Finasteride                                    | -6% ± 11% (9%)  | -3% ± 9% (8%)    | -11% ± 9% (13%)  |
| Dose A                                         | 4% ± 8% (6%)    | 3% ± 5% (5%)     | -5% ± 11% (9%)   |
| Dose B                                         | -5% ± 11% (9%)  | 0% ± 5% (4%)     | -7% ± 6% (6%)    |
| Box Model                                       | Control         | 0% ± 4% (3%)     | 3% ± 5% (5%)     | -11% ± 10% (11%)|
| Finasteride                                    | 3% ± 11% (9%)   | -2% ± 5% (4%)    | -9% ± 5% (10%)   |
| Dose A                                         | 2% ± 6% (4%)    | 0% ± 9% (6%)     | -4% ± 7% (7%)    |
| Dose B                                         | 2% ± 12% (9%)   | 1% ± 6% (5%)     | -7% ± 5% (6%)    |

Table 3.3: Relative error prostate volumes by 3rd set of models during treatment.

volume as measured by MRI with the water-displacement method. Both the in vivo (MRI) and ex vivo (necropsy) states of the prostate closely estimated prostate volume. The correlation we found between post-necropsy volumes and non-invasive volume segmentation of MRI data sets is consistent with the results from other groups, supporting the latter as a reliable assessment approach [62]. It is also worth mentioning the physiologic changes that take place after necropsy. At this time, the gland is no longer perfused or affected by the influence of surrounding tissues and has no neural integrity, all of which may lead to the overestimation of prostate volume by the MRI volume segmentation.

For prostate volume estimation, the model approaches estimate prostate volumes by measuring diameters at several specific locations and applying a model for the prostate shape. We used three different sets of models assessing the volume based
on up to eight diameters. By comparing the correlation coefficients, we can see that the 3rd set of models is superior to the 1st and 2nd set of models. The fact that the best model relies on measurements of diameters in two different directions may be indicative that measurements performed in only one plane are not sufficient enough to estimate different prostate shapes accurately. This agrees with the findings of Sosna et al [62] and Eri et al. [19], which reported an improvement in volume estimation based on measuring diameters in different slice orientations. However, there may be geometric abnormalities not taken into account by measuring diameters in planar slices, e.g. a lobulated prostate gland (such as a hypertrophied median lobe) which may not be best depicted in a true axial or coronal plane, but rather in an oblique plane.

The application of the 3rd set of models to the data-sets during treatment gave reliable prostate volume prediction results for the four groups and the models gave comparable prostate volume prediction errors. The Cube model and the Box model used eight diameters, while the Two-ellipsoid model only used 6 diameters A0, A1, A3, C0, C1 and C3. We would like to select the Two-ellipsoid model as the best model.

Because of the smaller size of the beagles, the standard head coil was sufficient for imaging the beagle’s prostate, allowing for imaging in its natural shape. For current state-of-the-art investigation of human prostates, endorectal coils are frequently used to improve image quality and spatial resolution [22]. The use of this kind of coil leads to a deformation of the prostate, so the derived models may need some adjustments to be applicable. However, our initial observation indicates that pelvic imaging at 3T
will generate images suitable for performing comparable studies in patients without
the need for an endorectal coil.

In conclusion, MRI-based prostate segmentation is feasible for prostate volume
determination, and can be considered validated with the correlation to post necropsy
volumes. Planar, diameter measurements can also be reliably used for accurate vol-
ume estimation based on the proposed model. This may offer an approach to assess
small changes in prostate volume, which appears when monitoring pharmacotherapy.
CHAPTER 4

PHARMACOKINETIC (PK) MODELS IN DCE-MRI

4.1 Introduction

To evaluate different pharmacokinetic models for fitting the DCE-MRI data of beagle prostate. Twenty-four male beagles with benign prostatic hyperplasia were enrolled in a drug trial. Two baseline MRI examination and three follow-ups were performed on a clinical 1.5 T MRI system using DCE-MRI for the assessment of prostate microcirculation. Four types of regions of interest (ROIs) were drawn on the periurethral region, parenchymal region, muscle and external iliac artery. Five pharmacokinetic models were evaluated for fitting the DCE-MRI datasets and characterizing microcirculation. The main difference of these models is based on the arterial input function assumption: 1st model (Workie’s model) [71] assumes an immediate wash-in and mono-exponential decay function; 2nd model (Extended Workie’s model) assumes an immediate wash-in and bi-exponential decay function; 3rd model (Brix’s model) [9] assumes a gradual wash-in with contrast agent injection duration and mono-exponential decay function; 4th model (Extended Brix’s model) assumes a gradual wash-in and bi-exponential decay function; 5th model (Larsson’s model) [36] takes the time-signal intensity curve from the external iliac artery ROI as AIF. The
goodness-of-fit was defined by $R^2$ with 1 as exact fit. The reproducibility of these parameters was examined in the double baselines using ANOVA-based coefficient of variation ($wCV$). The average $R^2$ is 0.948 for the 1st model, 0.955 for the 2nd model, 0.949 for the 3rd model, 0.955 for the 4th model, and 0.916 for the 5th model. For the pharmacokinetic parameters $K^{trans}$ and $A$, the extended Brix’s model (4th model) has smallest $wCV$ for the muscle, parenchymal, and periurethral ROIs. For the pharmacokinetic parameter $k_{ep}$, Larsson’s model (5th model) gives smallest $wCV$ for the muscle, parenchymal, and periurethral ROIs. Models without AIF (1st to 4th model) give better goodness-of-fit than the model with AIF from external iliac artery. Goodness-of-fit are better for the extended model. The pharmacokinetic parameter $A$ may be used to differentiate different tissues because of smallest overlap.

4.2 Materials and Methods

4.2.1 Pharmacokinetic Models

These most commonly used pharmacokinetic models are based on the exchange of contrast agent between two compartments: one compartment is blood plasma space; the other compartment is extravascular extracellular space (EES) as shown in Figure 4.1. The volume transfer rate from the blood plasma to the EES is defined as transfer constant ($K^{trans}$), and the volume transfer rate from the EES to the blood plasma is defined as rate constant ($k_{ep}$) [9]. The general equation describing the changes of the tracer concentration in tissue is obtained as

$$\frac{dC_t}{dt} = K^{trans}C_p - k_{ep}C_t,$$  (4.1)

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where $C_t$ is the tracer concentration in tissue and $C_p$ tracer concentration in blood plasma [67]. Based on the general equation of tracer kinetics, different pharmacokinetic models use different assumptions to solve the equation. The solution of the equation is then used to fit the real time-signal intensity curves from dynamic images. The fitting methods can be generally classified into two types: “direct-fit” type and “input-fit” type. The “direct-fit” type of models assumes a plasma concentration function and directly fit the time-signal intensity curve [66]. The “input-fit” type of models uses the arterial input function (AIF) and/or venous input function (VIF) from regions of interest to fit the time-signal intensity curve. Four “direct-fit” types of model (1st-4th model) and one “input-fit” type of model (5th model) will be investigated and compared in this study.

### 4.2.2 1st Pharmacokinetic Model: Workie’s model

Some “direct-fit” models assume a mono-exponential decay plasma curve with two plasma parameters [71], as the following

$$C_p(t) = \begin{cases} 
0 & 0 \leq t \leq t_{lag} \\
C_p0 e^{-k_{el}(t-t_{lag})} & t_{lag} \leq t 
\end{cases}, \quad (4.2)$$

where $t_{lag}$ is lag time when the contrast agent arrives to the tissue. Under the assumption of Equation 4.2, the solution to tracer kinetic Equation 4.1 is obtained as

$$C_t(t) = \begin{cases} 
0 & 0 \leq t \leq t_{lag} \\
\frac{C_p0}{k_{el}-k_{ep}} [e^{-k_{ep}(t-t_{lag})} - e^{-k_{el}(t-t_{lag})}] & t_{lag} \leq t 
\end{cases}, \quad (4.3)$$

For low tracer concentration, the MR signal intensity $S(t)$ in DCE-MRI has the following relationship to the contrast agent concentration $C(t)$:

$$\frac{S(t)}{S_0} - 1 \approx T_{10} r_1 C(t) \quad (4.4)$$

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Figure 4.1: The two-compartment pharmacokinetic model describes the exchange of the extracellular contrast agent between the blood plasma compartment and extravascular extracellular compartment.
where $S_0$ is the signal intensity before the arrival of the contrast agent, $T_{10}$ is the value of $T_1$ without contrast agent, and $r_1$ is relaxivity of $T_1$ [71, 66]. Substituting this equation to Equation 4.3, the equation for fitting the time-signal intensity curve can be finally obtained as

$$\frac{S(t)}{S_0} - 1 \approx \left\{ \begin{array}{ll}
0 & 0 \leq t \leq t_{lag} \\
\frac{A}{\tau(k_{el} - k_{ep})} [e^{-k_{ep}(t-t_{lag})} - e^{-k_{el}(t-t_{lag})}] & t_{lag} \leq t
\end{array} \right., \quad (4.5)$$

where $A$ is equal to $T_{10} r_1 C_p^0 K_{trans}$ with $T_{10}$ in tissue and $r_1$ as the $r_1$ in tissue. This model consisting of four parameters ($A$, $k_{ep}$, $k_{el}$, and $t_{lag}$) has been used in monitoring the chemotherapy of breast cancer [3], and in monitoring the degree of inflammation and clinical outcome of arthritis in children [71].

### 4.2.3 2nd Pharmacokinetic Model: Extended Workie’s model

This “direct-fit” model assumes a limited bi-exponential decay plasma curve with three plasma parameters as

$$C_p(t) = \left\{ \begin{array}{ll}
0 & 0 \leq t \leq t_{lag} \\
C_p^0 \sum_{i=1}^{2} \frac{1}{2} e^{-k_{el_i}(t-t_{lag})} & t_{lag} \leq t
\end{array} \right., \quad (4.6)$$

where $k_{el1}$ and $k_{el2}$ are the two decay factors. With this assumption of tracer concentration in blood plasma, the solution to the tracer kinetics Equation 4.1 is obtained as

$$C_I(t) = \left\{ \begin{array}{ll}
0 & 0 \leq t \leq t_{lag} \\
\sum_{i=1}^{2} \frac{C_p^0}{2(k_{el_i} - k_{ep})} [e^{-k_{ep}(t-t_{lag})} - e^{-k_{el_i}(t-t_{lag})}] & t_{lag} \leq t
\end{array} \right., \quad (4.7)$$

The equation used to fit the time-signal intensity curves is given as

$$\frac{S(t)}{S_0} - 1 \approx \left\{ \begin{array}{ll}
0 & 0 \leq t \leq t_{lag} \\
\frac{A}{\sum_{i=1}^{2} 2\tau(k_{el_i} - k_{ep})} [e^{-k_{ep}(t-t_{lag})} - e^{-k_{el_i}(t-t_{lag})}] & t_{lag} \leq t
\end{array} \right.. \quad (4.8)$$

This solution includes five parameters ($A$, $k_{ep}$, $k_{el1}$, $k_{el2}$, and $t_{lag}$). All the five parameters were obtained by fitting the time-signal intensity curves in tissue.
4.2.4 3rd Pharmacokinetic Model: Brix’s Model

This “direct-fit” model assumes a mono-exponential decay plasma curve, which is described by the equation [9]

\[
\frac{dC_p}{dt} = \frac{K_{in}}{V_1} - k_{el}C_p,
\]  

(4.9)

Where \( V_1 \) is the volume of the blood plasma compartment. The solution has two plasma parameters, as the following

\[
C_p(t) = \begin{cases} 
0 & 0 \leq t \leq t_{lag} \\ 
\frac{K_{in}}{V_1 k_{el}} (1 - e^{-k_{el}(t-t_{lag})}) & t_{lag} \leq t \leq t_{lag} + \tau \\ 
\frac{K_{in}}{V_1 k_{el}} (e^{k_{el} \tau} - 1)e^{-k_{el}(t-t_{lag})} & t_{lag} + \tau \leq t 
\end{cases}
\]  

(4.10)

Under the assumption of Equation 4.10, the solution to tracer kinetic Equation 4.1 is obtained as

\[
\frac{S(t)}{S_0} - 1 \approx \begin{cases} 
A \tau \left\{ \frac{k_{el}(1 - e^{-k_{el}(t-t_{lag})})}{k_{el}(k_{el}-k_{el})} - \frac{(1 - e^{-k_{el}(t-t_{lag})})}{k_{el}-k_{el}} \right\} & 0 \leq t \leq t_{lag} \\ 
A \tau \left\{ \frac{k_{el}(e^{k_{el} \tau} - 1)e^{-k_{el}(t-t_{lag})}}{k_{el}(k_{el}-k_{el})} - \frac{(e^{k_{el} \tau} - 1)e^{-k_{el}(t-t_{lag})}}{k_{el}-k_{el}} \right\} & t_{lag} \leq t \leq t_{lag} + \tau \\ 
A \tau \left\{ \frac{k_{el}(e^{k_{el} \tau} - 1)e^{-k_{el}(t-t_{lag})}}{k_{el}(k_{el}-k_{el})} - \frac{(e^{k_{el} \tau} - 1)e^{-k_{el}(t-t_{lag})}}{k_{el}-k_{el}} \right\} & t_{lag} + \tau \leq t 
\end{cases}
\]  

(4.11)

where \( A \) is proportional to \( K_{trans} \). This model consists of four parameters (\( A, k_{el}, k_{el}, \) and \( t_{lag} \)) [9].

4.2.5 4th Pharmacokinetic Model: Extended Brix’s Model

This “direct-fit” model assumes a limited bi-exponential decay plasma curve with three plasma parameters as

\[
C_p(t) = \begin{cases} 
0 & 0 \leq t \leq t_{lag} \\ 
\sum_{i=1}^{2} \frac{1 - e^{-k_{el_i}(t-t_{lag})}}{k_{el_i}} & t_{lag} \leq t \leq t_{lag} + \tau \\ 
\sum_{i=1}^{2} \frac{(e^{k_{el_i} \tau} - 1)e^{-k_{el_i}(t-t_{lag})}}{k_{el_i}} & t_{lag} + \tau \leq t 
\end{cases}
\]  

(4.12)
where $k_{el1}$ and $k_{el2}$ are the two decay factors. With this assumption of tracer concentration in blood plasma, the solution to the tracer kinetics Equation 4.1 is obtained.

The solution used to fit the time-signal intensity curves is given as

$$
\frac{S(t)}{S_0} - 1 \approx \begin{cases} 
\frac{A}{2\tau} \sum_{i=1}^{2} \left\{ \frac{k_{ep} (1 - e^{-k_{el1} (t - t_{lag})})}{k_{el1} (k_{ep} - k_{el1})} - \frac{(1 - e^{-k_{ep} (t - t_{lag})})}{k_{ep} - k_{el1}} \right\} & 0 \leq t \leq t_{lag} \\
\frac{A}{2\tau} \sum_{i=1}^{2} \left\{ \frac{k_{ep} (e^{k_{el1} \tau} - 1) e^{-k_{el2} (t - t_{lag})}}{k_{el1} (k_{ep} - k_{el1})} - \frac{(e^{k_{ep} \tau} - 1) e^{-k_{ep} (t - t_{lag})}}{k_{ep} - k_{el1}} \right\} & t_{lag} \leq t \leq t_{lag} + \tau \\
t_{lag} + \tau \leq t & \text{(4.13)}
\end{cases}
$$

This solution includes five parameters ($A$, $k_{ep}$, $k_{el1}$, $k_{el2}$, and $t_{lag}$). All the five parameters were obtained by fitting the time-signal intensity curves in tissue.

### 4.2.6 5th Pharmacokinetic Model: Larsson’s Model

The 5th model is an ‘input-fit’ model using the AIF from ROIs on artery. The tracer kinetic Equation 4.1 can be written into a convolution integral form as [36]

$$
C_t(t) = K^{\text{trans}} \int_0^t C_p(t') e^{-k_{ep}(t-t')} dt',
$$

(4.14)

By considering the case that the tissue might include the fraction of the plasma space, the above equation can be extended to the following equation [43]

$$
C_t(t) = K^{\text{trans}} \int_0^t C_p(t') e^{-k_{ep}(t-t')} dt' + f_{PV} C_p(t),
$$

(4.15)

where $f_{PV}$ is the fractional plasma volume of the tissue with the range from 0 to 1.

The tracer concentration in blood plasma $C_p(t)$ can be obtained from the ROI in the artery of dynamic images as the arterial input function (AIF). $C_p(t)$ can be obtained from the MR signal intensity $S_{AIF}(t)$:

$$
C_p(t) = \frac{1}{T_{10p} T_{1p}} \left( \frac{S_{AIF}(t)}{S_{0AIF}} - 1 \right),
$$

(4.16)
where $S_{0AIF}$ is the signal intensity in blood plasma before the arrival of the contrast agent, $T_{10p}$ is the value of $T_1$ in blood plasma without contrast agent, and $r_{1p}$ is the relaxivity of $T_1$ in blood plasma. The Equation 4.15 can be expressed by the MR signal intensity in tissue and in blood plasma as

$$\frac{S(t)}{S_0} - 1 = K^{\text{trans}'} \int_0^t \left( \frac{S_{AIF}(t)}{S_{0AIF}} - 1 \right) e^{-k_{ep}(t-t')} dt' + f_{PV}' \left( \frac{S_{AIF}(t)}{S_{0AIF}} - 1 \right), \quad (4.17)$$

with the following relationships:

$$K^{\text{trans}'} = \frac{T_{10t}}{T_{10p} r_{1p}} K^{\text{trans}}, \quad (4.18)$$

and

$$f_{PV}' = \frac{T_{10t}}{T_{10p} r_{1p}} f_{PV}, \quad (4.19)$$

The curve-fitting routine can generate three parameters ($K^{\text{trans}'}$, $k_{ep}$, $f_{PV}'$) by doing convolution integral and finding the best fit to the tissue signal intensity. In the following text, $K^{\text{trans}'}$ is denoted as $K^{\text{trans}}$ for simplicity.

### 4.2.7 Summary of Pharmacokinetic Models

The main difference of these five pharmacokinetic models is the arterial input function ($C_p(t)$) assumption. The 1st and 2nd models skip the wash-in phase of the arterial input function, while the 3rd and 4th model have the the wash-in phase with time duration of contrast agent injection duration ($\tau$). The original models (1st and 3rd) assume mono-exponential decay during wash-out phase in artery, while the extended models (2nd and 4th) assume bi-exponential decay. The last model (5th) directly takes the time-signal intensity curves from artery, such as external iliac artery, as the arterial input function. The comparison among these pharmacokinetic models is illustrated in Figure 4.2.
Different AIF Assumption in 5 PK models

1. Workie’s Model
   - Immediate wash-in
   - Mono-exponential decay during wash-out

2. Extended Workie’s Model
   - Immediate wash-in
   - Limited bi-exponential decay during wash-out

3. Brix’s Model
   - Wash-in phase with injection duration $\tau$
   - Mono-exponential decay during wash-out

4. Extended Brix’s Model
   - Wash-in phase with injection duration $\tau$
   - Limited bi-exponential decay during wash-out

5. Larsson’s Model
   - Real AIF from ROI on external iliac artery

Figure 4.2: Five models have different assumptions of arterial input function $C_p(t)$. The first two models assume immediate wash-in and exponential decay during wash-out phase; the second two models assume gradual wash-in and exponential decay. The last model assumes that the AIF is identical to the time-signal intensity curve from artery ROI.
4.2.8 Fitting Algorithms

The DCE-MRI data analysis was performed using an in-house developed software based on IDL (Interactive Data Language, Research Systems Inc., Boulder, CO). The model-based parameters for the ROIs were determined by least-squares fitting of the measured data. The fitting algorithm is the Levenberg-Marquardt least-squares minimization (MINPACK-1) method of fitting a user defined function, implemented by the IDL programs MPFIT and MPFITFUN, and available online at http://cow.physics.wisc.edu/~craigm/idl/fitting.html. The application of this fitting algorithm to DCE-MRI data was investigated and discussed in details [1].

4.2.9 Goodness-of-fit

Four types of region of interest (ROI) were drawn on dynamic images: parenchymal and periurethral regions in the largest cross section of the prostate, muscle ROI and external iliac artery (Figure 4.3).

The model-based parameters for the ROIs were determined by least-squares fitting of the measured data. The fit to experimental data provided by the pharmacokinetic model will be calculated using the parameter $R^2$ [20]

$$R^2 = 1.0 - \frac{SS_{error}}{SS_{total}},$$  \hspace{1cm} (4.20)

where $SS_{error}$ is the sum of the squares of the distance of the experimental data points from the best-fit curve determined from the model, and $SS_{total}$ is the sum of the squares of the distances of the data points from a horizontal line through the mean of all experimental data points. When $R^2$ equals 1.0, all points will be exactly positioned on the best-fit curve without any scatter. When $R^2$ equals 0, the best-fit
Figure 4.3: Four types of ROI were defined on the DCE-MRI data sets. Two ROIs were defined in the prostate: periurethral ROI and parenchymal ROI. Muscle ROI and external iliac artery ROI were drawn surrounding the prostate. The external iliac artery ROI was used in 5th model as arterial input function. The time-signal intensity curve of these ROIs were plotted above the images.
curve fits the experimental data no better than a horizontal line going through the mean of the experimental data points.

### 4.2.10 Reproducibility Analysis

The two baseline MR studies were used for reproducibility analysis of the pharmacokinetic parameters. For each subject, the difference between the two baseline measurements of a pharmacokinetic parameter, \( d \), was calculated. The following statistical measures of reproducibility were obtained from a one-way analysis of variance (ANOVA) on the original data [51]. The mean squared difference \( dSD \) was calculated from

\[
dSD = \sqrt{\frac{\sum d^2}{n}},
\]  

The within-patient standard deviation \( (wSD) \) equals \( dSD \) divided by the square root of 2

\[
wSD = \frac{dSD}{\sqrt{2}},
\]

The repeatability of a pharmacokinetic parameter, \( r \), was calculated as 2.77 times \( wSD \)

\[
r = 2.77 \cdot wSD,
\]

The within patient coefficient of variation \( (wCV) \) was obtained by dividing the \( wSD \) by the global mean for each pharmacokinetic parameter

\[
wCV = \frac{wSD}{\text{GlobalMean}},
\]

### 4.3 Results

The Goodness-of-fit \( R^2 \) of the five pharmacokinetic models were plotted in Figure 4.4. All \( R^2 \) are close to 1, i.e. within 0.85 and 1. The average \( R^2 \) is 0.948 for the
Figure 4.4: The goodness-of-fit of the five pharmacokinetic models for the parenchymal, periurethral and muscle ROIs during the two baseline measurements (B01 and B02). The figures at the bottom show the example curve fit by the 1st and 2nd models (left), 3rd and 4th (middle), and 5th model (right figure). The extended model (2nd and 4th) models gave the best curve fit and highest goodness of fit $R^2$.

1st model, 0.955 for the 2nd model, 0.949 for the 3rd model, 0.955 for the 4th model, and 0.916 for the 5th model.

The reproducibility analysis results are shown in Table 4.1 and Table 4.2. For the pharmacokinetic parameter $K_{\text{trans}}$ and $A$, the extended Brix’s model (4th model) has smallest $wCV$ for the muscle, parenchymal, and periurethral ROIs. For the
Figure 4.5: The plot of the parameter $A$ in Extended Brix’s model in B01 against those in B02.

The pharmacokinetic parameter $k_{ep}$, Larsson’s model (5th model) gives smallest $wCV$ for the muscle, parenchymal, and periurethral ROIs.

The pharmacokinetic parameters in B01 against B02 is in Figure 4.5, 4.6, 4.7, 4.8, 4.9, 4.10. For the three type of tissues (muscle, parenchymal tissue, and periurethral tissue), $A$ in extended Brix’s model (4th) model has smallest overlap.
Reproducibility of $K_{trans}$ and $A$

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$K_{trans}$</th>
<th>$A$ (2nd model)</th>
<th>$A$ (4th model)</th>
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<tr>
<td>Muscle</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Global Mean</td>
<td>0.119</td>
<td>1.431</td>
<td>0.611</td>
</tr>
<tr>
<td>Mean Difference ± SD</td>
<td>0.008±0.055</td>
<td>0.718±1.635</td>
<td>-0.109±0.292</td>
</tr>
<tr>
<td>$dSD$</td>
<td>0.054</td>
<td>1.754</td>
<td>0.306</td>
</tr>
<tr>
<td>$wSD$</td>
<td>0.038</td>
<td>1.241</td>
<td>0.216</td>
</tr>
<tr>
<td>Repeatability $r$</td>
<td>0.106</td>
<td>3.436</td>
<td>0.599</td>
</tr>
<tr>
<td>$wCV$(%$)$</td>
<td>32.3</td>
<td>86.7</td>
<td>35.4</td>
</tr>
<tr>
<td>Parenchymal Region</td>
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<td></td>
<td></td>
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<tr>
<td>Global Mean</td>
<td>1.069</td>
<td>19.309</td>
<td>2.803</td>
</tr>
<tr>
<td>Mean Difference ± SD</td>
<td>-0.018 ± 0.463</td>
<td>1.374 ± 10.030</td>
<td>0.181 ± 0.441</td>
</tr>
<tr>
<td>$dSD$</td>
<td>0.454</td>
<td>9.914</td>
<td>0.468</td>
</tr>
<tr>
<td>$wSD$</td>
<td>0.321</td>
<td>7.011</td>
<td>0.331</td>
</tr>
<tr>
<td>Repeatability $r$</td>
<td>0.888</td>
<td>19.419</td>
<td>0.916</td>
</tr>
<tr>
<td>$wCV$(%$)$</td>
<td>30.0</td>
<td>36.3</td>
<td>11.8</td>
</tr>
<tr>
<td>Periurethral Region</td>
<td></td>
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<td></td>
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<tr>
<td>Global Mean</td>
<td>2.531</td>
<td>26.822</td>
<td>7.133</td>
</tr>
<tr>
<td>Mean Difference ± SD</td>
<td>0.007 ± 1.353</td>
<td>1.825 ± 11.939</td>
<td>0.509 ± 1.774</td>
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<td>$dSD$</td>
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<td>1.280</td>
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<tr>
<td>Repeatability $r$</td>
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<td>23.170</td>
<td>3.545</td>
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<tr>
<td>$wCV$(%$)$</td>
<td>37.0</td>
<td>31.2</td>
<td>17.9</td>
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Table 4.1: The reproducibility analysis of the extended models and the 5th model. The pharmacokinetic parameter $K_{trans}$ from the 5th model and $A$ from the 2nd and 4th model were listed.
<table>
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<th>Parameter</th>
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<td>$k_{ep}$ (5th model)</td>
<td>$k_{ep}$ (2nd model)</td>
<td>$k_{ep}$ (4th model)</td>
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<tr>
<td>Global Mean</td>
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<td>1.659</td>
<td>2.400</td>
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<tr>
<td>Mean Difference ± SD</td>
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<td>0.900 ± 2.002</td>
<td>1.618 ± 3.183</td>
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<tr>
<td>$dSD$</td>
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<tr>
<td>$wSD$</td>
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<td>1.525</td>
<td>2.483</td>
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<tr>
<td>Repeatability $r$</td>
<td>0.729</td>
<td>4.223</td>
<td>6.877</td>
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<tr>
<td>$wCV(%)$</td>
<td>54.7</td>
<td>91.9</td>
<td>103.4</td>
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<table>
<thead>
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<td>$k_{ep}$ (2nd model)</td>
<td>$k_{ep}$ (4th model)</td>
<td></td>
</tr>
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<tr>
<td>Mean Difference ± SD</td>
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<td>$dSD$</td>
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<tr>
<td>$wSD$</td>
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<td>2.137</td>
<td>2.615</td>
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<tr>
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<td>5.918</td>
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<td>$wCV(%)$</td>
<td>20.4</td>
<td>30.6</td>
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<table>
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<th></th>
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</thead>
<tbody>
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<td>$k_{ep}$ (2nd model)</td>
<td>$k_{ep}$ (4th model)</td>
<td></td>
</tr>
<tr>
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<td>3.743</td>
<td>4.743</td>
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<tr>
<td>Mean Difference ± SD</td>
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<td>-0.054 ± 2.329</td>
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<tr>
<td>$dSD$</td>
<td>0.622</td>
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</tr>
<tr>
<td>$wSD$</td>
<td>0.440</td>
<td>1.612</td>
<td>2.377</td>
<td></td>
</tr>
<tr>
<td>Repeatability $r$</td>
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<td>6.585</td>
<td></td>
</tr>
<tr>
<td>$wCV(%)$</td>
<td>35.3</td>
<td>43.1</td>
<td>50.1</td>
<td></td>
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Table 4.2: The reproducibility analysis of the extended models and the 5th model. The pharmacokinetic parameter $k_{ep}$ from the 5th model, 2nd and 4th model was listed.
Figure 4.6: The plot of the parameter $A$ in Extended Workie’s model in B01 against those in B02.
Figure 4.7: The plot of the parameter $K^{\text{trans}}$ in Larsson’s model in B01 against those in B02.
Figure 4.8: The plot of the parameter $k_{ep}$ in Extended Brix’s model in B01 against those in B02.
Figure 4.9: The plot of the parameter $k_{ep}$ in Extended Workie’s model in B01 against those in B02.
Figure 4.10: The plot of the parameter $k_{ep}$ in Larsson’s model in B01 against those in B02.
4.4 Discussions

The first four models (1st to 4th) models gave higher $R^2$ than the 5th model. The extended model (2nd and 4th) showed higher $R^2$ than the original model (1st and 3rd) respectively. Because the prostate is highly vascularized, the extended models (2nd and 4th model) will likely give higher goodness-of-fit than 1st and 3rd model. For the surrounding tissue, such as muscle, the extended model will give similar goodness-of-fit and be close to the non-extended model. The 5th model used arterial input function from artery ROI to normalize experimental plots, so high reproducibility of the phamcokinetic paraarmters, such as $k_{ep}$ was given.

The smallest overlap among different tissues given by $A$ in the 4th model may be used to differentiate substructures in the prostate, such as central zone, transition zone, peripheral zone, and muscular fibers, etc.

The 5th model directly use the time-signal intensity curve from external iliac artery ROI as the arterial input function. The cross section region of the artery is small, which might cause some partial volume artifact to the placement of arterial ROI. Workie’s model and the extended Workie’s model do not use injection duration ($\tau$) as parameter. Since the injection duration is difficult to measure for hand-injection and is generally no tag for record in DICOM file, these models might be easier to implement than Brix’s model and the extended Brix’s model.

In conclusion, the models without AIF (1st to 4th model) give better goodness-of-fit than the model with AIF from external iliac artery. Goodness-of-fit are better for the extended model. The pharmacokinetic parameter $A$ may be used to differentiate different tissues because of smallest overlap.
CHAPTER 5

PK PARAMETERS AS PROSTATE VOLUME REDUCTION PREDICTOR

5.1 Introduction

We sought to assess the possibility of using pharmacokinetic parameters as a predictor of response to benign prostatic hyperplasia (BPH) pharmacotherapy via a randomized, placebo-controlled, animal preclinical trial using dynamic contrast-enhanced MRI. Twelve male beagles with BPH were enrolled in a preclinical experimental drug trial and divided into two randomized groups with six beagles each: one drug (finasteride) group and one placebo (control) group. The pharmacokinetic parameters, maximum enhancement ratio (MER), transfer constant and rate constant, were assessed to characterize the microcirculation in the parenchymal zone. The time-signal intensity curve from the external iliac artery was used as the arterial input function. The correlation between baseline evaluations (prostate volume and pharmacokinetic parameters) and therapy-induced prostate volume changes under finasteride treatment were assessed. The changes in prostate volume at the end of the trial exhibited a significant linear correlation to the initial parenchymal MER ($p < 0.02$) in the finasteride group. Larger prostate volume reductions coincided with smaller initial
parenchymal MER. These findings show considerable promise of using parenchymal MER as a predictor of response to BPH pharmacotherapy with finasteride.

5.2 Materials and Methods

5.2.1 Image Analysis

The prostate volume segmentation was completed using a semi-automated method that combined T1 and T2-weighted images in Chapter 3. The DCE-MRI data analysis was performed using an in-house developed software based on IDL (Interactive Data Language, Research Systems Inc., Boulder, CO). Two regions of interest (ROIs) were defined on dynamic images: one in the external iliac artery and a second in the parenchymal zone. The glandular tissue comprised the parenchymal ROI in the slice with the largest prostate cross-section area, as shown in Figure 5.1, in order to facilitate the comparison between baseline and follow-up images [28]. The ROIs were manually shifted to compensate for subject motion during scans.

Both semi-quantitative and model-based parameters were obtained from the time-signal intensity data of the parenchymal ROIs. Baseline signal intensity was calculated from the initial three time points prior to contrast agent injection. The maximum enhancement ratio (MER [dimensionless]) was calculated as the increase of the maximum signal intensity and baseline signal intensity (Figure 5.1C) [18]. The 5th model (‘input-model’ model in Chapter 4) including two parameters, transfer constant \( K^{\text{trans}} \ [\text{min}^{-1}] \) and exchange rate constant \( k_{ep} \ [\text{min}^{-1}] \), was fitted to the tissue time-signal intensity curve by doing a convolution of the external iliac arterial time-signal intensity curve and the residue impulse response function \( K^{\text{trans}} e^{-k_{ep}t} \), where \( t \) is time with the initial condition, \( t = 0 \). Transfer constant \( K^{\text{trans}} \) is the
Figure 5.1: The parenchymal regions of interest (ROIs), drawn in the slice with maximum extension of the prostate and the corresponding evaluation curves. (A) The placement of parenchymal ROI in Baseline #1 of one subject with larger parenchymal MER (Subject E in Figure 5.2). (B) The placement of parenchymal ROI in Baseline #1 of one subject with smaller parenchymal MER (Subject F in Figure 5.2). (C) The time-enhancement ratio curves obtained from the parenchymal ROIs. Subject E was shown to have higher parenchymal MER (MER = 2.65) than subject F (MER = 2.08) in Baseline #1.
product of the extraction fraction across the capillary membranes and the perfusion through the capillaries. Exchange rate constant $k_{ep}$ determines the washout rate from the extravascular extracellular space (EES) back into the blood plasma [67].

5.2.2 Data processing and statistical analysis

The Wilcoxon signed-rank test was used to check significant differences between two sets of related parameters. In order to reduce measurement errors, the average of the baseline (pre-finasteride treatment) values was defined as the initial value if there was no significant difference between the two baseline measurements. The change in prostate volume was defined as the percentage change between the initial prostate volume and the prostate volume during treatment at weeks 4, 8, and 12. The initial pharmacokinetic parameters were evaluated for the potential of predicting the final changes in prostate volume at the end of the trial. The Pearson linear correlation coefficient $r$ (two-tailed test) was used to determine whether a linear relationship existed between the initial parameters and prostate volume changes. Statistical significance was defined as $p < 0.05$. All data were analyzed using SPSS statistical software (SPSS Inc., Chicago, IL).

5.3 Results

There was no significant difference between the two sets of baseline prostate volume and pharmacokinetic parameters as depicted in Table 5.1. All subjects were well matched for prostate volume, parenchymal MER, parenchymal $K^{trans}$ and parenchymal $k_{ep}$ between the two baselines.

The subjects in the control group did not experience significant prostate volume changes: $1.9\% \pm 5.7\%$ in week 4 ($p = 0.60$), $-0.1\% \pm 7.5\%$ in week 8 ($p = 0.92$),
### Summary of baseline results

<table>
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<th>Baseline #1</th>
<th>Baseline #2</th>
<th>p Value</th>
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<td>Prostate vol. ± SD (cc)</td>
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<td>Parenchymal MER ± SD</td>
<td>2.63 ± 0.43</td>
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<td>Parenchymal $K_{\text{trans}}$ ± SD (min$^{-1}$)</td>
<td>0.93 ± 0.34</td>
<td>0.92 ± 0.20</td>
<td>0.937</td>
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<tr>
<td>Parenchymal $k_{ep}$ ± SD (min$^{-1}$)</td>
<td>1.33 ± 0.26</td>
<td>1.29 ± 0.33</td>
<td>0.937</td>
</tr>
</tbody>
</table>

Table 5.1: Summary of prostate volume and parenchymal pharmacokinetic parameters in two baseline MR measurements.

and -0.7% ± 10.5% in week 12 ($p = 0.75$). All subjects in the finasteride group experienced significant prostate volume reductions (-35% ± 13% in week 4, -40% ± 13% in week 8, and -47% ± 11% in week 12, all $p$’s < 0.05) as shown in Figure 5.2. In the finasteride group, the prostate volume reduction varied from 33% to 66% at the end of the trial.

In the finasteride group, a significant linear correlation was found between the initial parenchymal MER and the prostate volume reduction in week 12 ($r = 0.91$, $p < 0.02$, Figure 5.3). Positive values of the Pearson linear correlation coefficient, $r$, shows that subjects with smaller initial parenchymal MER exhibited larger reductions in the prostate volume. The prostate volume reductions in week 12 in the finasteride group were not found to be significantly correlated to the initial prostate volume ($p = 0.44$), the initial parenchymal $K_{\text{trans}}$ ($p = 0.96$), or the initial parenchymal $k_{ep}$ ($p = 0.79$).
Figure 5.2: Changes in prostate volume in finasteride group. All six subjects (A-F) experienced prostate volume reduction (-33% ~ -66% in week 12). Subjects C, D, and E had dramatic volume reduction in week 4. Subjects B and F had continuous prostate volume reduction in weeks 4, 8, and 12.
Figure 5.3: The Pearson linear correlation between initial parenchymal MER and final prostate volume reduction in week 12 ($p < 0.02$). The fitted equation is $y = 0.5x - 1.6$ with $x$ as the initial parenchymal MER and $y$ the change in prostate volume in week 12.
5.4 Discussions

Many studies have been carried out in order to find a capable method for selecting appropriate patients for BPH pharmacotherapy. From meta-analysis of six trials involving 2601 men with BPH, Boyle et al suggested finasteride is most effective in men with large prostate [7]. Marks et al identified a linear relationship between the pretreatment transition zone epithelial content and the prostate volume reduction [39]. Roehrborn et al showed an ever-increasing net drug benefit with increasing serum PSA values from the large scale PLESS and dutasteride phase III trials [57, 58]. There are several problems associated with these methods. Some methods, such as quantitative histology, are invasive and thus not applicable to clinical routine practice. Some methods, lacking a strong linear relation between the predictors and volume reductions, only have statistical meaning, and therefore the outcome is difficult to predict for the individual patient.

Our results show that the parenchymal MER is linearly correlated to changes in prostate volume. The subjects with smaller parenchymal MER exhibited greater prostate volume reduction; that is, subjects having smaller parenchymal MER seem to benefit more from pharmacotherapy with finasteride. Therefore, response to BPH therapy may be predicted based on the parenchymal MER. To explain the linear relationship between parenchymal MER and therapy-induced prostate volume reduction, we here propose the Apoptosis-induced Volume Reduction model. In general, as the 5α-reductase inhibitor finasteride causes the apoptosis of the epithelial cells, the intraprostatic pressure may compress the prostate and lead to the reduction in prostate volume.
The intravenous injection of extracellular contrast agent was shown to be an effective approach to non-invasively investigate the microvasculature and microcirculation of tissue. The parenchymal MER is affected by microvessel counts, vascular density, and the interstitial water space [67, 69]. Since the intraprostatic pressure may also compress the vasculature and decrease the interstitial water space, we can assume that prostate compressive pressure is inversely correlated to the parenchymal MER, i.e. the prostates with smaller parenchymal MER indicate higher intraprostatic pressure.

An increase in the number and size of the glands and ducts in BPH may increase the pressure inside the prostate [60]. On the contrary, the pharmacotherapy with finasteride induces atrophy and apoptosis in the prostate [61], which may destroy the force balance in the prostate. Since prostates with higher initial intraprostatic pressure might experience larger prostate volume reduction, based on the assumption that parenchymal MER is inversely correlated to intraprostatic pressure, we can draw the conclusion that prostates with smaller parenchymal MER might experience larger prostate reduction.

While our investigation was a prospectively-designed experimental preclinical study, it was limited by the number of subjects. Nevertheless, a significant linear correlation was demonstrated between the parenchymal MER and therapy-induced prostate volume reduction. The MER in the parenchyma region in the beagle prostate was found to correlate with subject response to pharmacotherapy in this study. Because of the anatomical differences between the human and dog prostate [63], different zones within the prostate should be investigated to find the corresponding region of interest that most closely correlates with prostate volume reduction to BPH pharmacotherapy.
In conclusion, the ability to select patients who would benefit most from certain dosage of BPH pharmacotherapy exists and appears explainable. As demonstrated by the Apoptosis-induced Prostate Volume Reduction model, our investigation revealed that the parenchymal MER in DCE-MRI exhibits a significant linear relationship to the change in prostate volume. These findings show great promise in using pharmacokinetic parameter as a predictor of subject response to 5α-reductase inhibitors.
CHAPTER 6

PK PARAMETERS AS PROSTATIC SUBURETHRAL MICROCIRCULATION BIOMARKER

6.1 Introduction

To assess the use of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) as a biologic marker of in-vivo changes in microcirculation in the prostatic suburethral region, twelve male beagles with spontaneous benign prostatic hyperplasia (BPH) were randomly allocated to two groups: one control group and one finasteride-treated group. Two baseline DCE-MRI examinations and three follow-ups were performed for the assessment of prostate microcirculation. The duration of treatment was 3 months. The pharmacokinetic parameters evaluated on prostatic suburethral areas included the maximum enhancement ratio (MER, [a.u.]), the time to maximum signal enhancement (T_{max}, \text{[min]}), amplitude (A, [a.u.]), and exchange rate constant (k_{ep}, \text{[min}^{-1}]). After completion of the therapeutic regimen, T_{max} was significantly longer in the finasteride group compared to controls (p < 0.01). The amplitude A and exchange rate constant k_{ep} decreased 39% and 34% respectively in the finasteride group at the end of the treatment, which significantly differed from the
control group ($p < 0.05$). DCE-MRI is capable of non-invasively assessing the prostatic microcirculation changes induced by finasteride. The pharmacokinetic parameters show considerable promise to be biomarkers in the development of BPH drugs such as 5α-reductase inhibitors by in-vivo monitoring the microvascular changes. A relevant clinical application could be the pretreatment assessment of finasteride effectiveness to reduce perioperative bleeding at transurethral resection of the prostate and in the treatment of hematuria.

6.2 Materials and Methods

6.2.1 Image Analysis

The DCE-MRI data analysis was performed using in-house developed software based on the IDL environment (Interactive Data Language, Research Systems Inc., Boulder, CO). The slices were selected covering the suburethral tissues in caudal prostate as depicted in Figure 6.1, where the 3-dimensional modeling of the prostate and the urethra was generated from axial T2-weighted MR images by the MIPAV (Medical Image Processing, Analysis, and Visualization) software [41]. The Regions of Interest (ROIs) were drawn on the caudal part of the prostate instead of the central part. This is because the central part is highly subject to deformation caused by external pressure such as rectal filling and changes in subject position. Three ROIs were defined on three consecutive slices covering the caudal part of the prostate: One ROI was drawn on the slice covering the urethra just outside of the prostate (Figure 6.2A), as a comparison to the other two on the slices that are within the prostate (Figure 6.2B and 6.2C). By going through all 32 time points, the ROIs were drawn in the center of the contrast-enhanced urethral region during peak enhancement.
Figure 6.1: The relative position of three slices bearing the prostatic suburethral ROIs in the 3-dimensional models of the prostate and the urethra obtained from T2-weighted images. The 3-dimensional model of the prostate is in pink color and part of the postprostatic urethra and the urethral outside the prostate is in slateblue color. Slice A is the slice covering the urethra immediately caudal of the prostate. Slices B and C are the slices covering the urethra in the caudal part of the prostate. The corresponding regions of interest and time-signal intensity curves are shown in Figure 6.2.

such as the time point 7 and 8 (Fig 6.2), furthermore, these ROIs for each time point were co-registered to compensate for subject motion during scans.

Two types of pharmacokinetic parameters were calculated from the time-signal intensity data $S(t)$ of the prostatic suburethral ROIs. One type is the semi-quantitative parameters including the maximum enhancement ratio (MER, [a.u.]) and the time to maximum signal enhancement $T_{max}$ (min). MER is defined as the maximum value of $S(t)/S_0 - 1$, and $T_{max}$ as the time lapse between the arrival of the contrast agent...
Figure 6.2: The three prostatic suburethral ROIs and their corresponding evaluation curves for the baseline ST1. The solid lines in the curve plots are the model-fit to the data. The dynamic images of the slice covering the urethral outside the prostate (A) and the slices covering the postprostatic urethra (B and C) at different time points (1, 5, 6, 7, 8, 15, and 31) are displayed below the time-signal intensity curve plots with the orange-colored region of interest (ROI).
and the point of maximum signal intensity, where $S_0$ is the baseline signal intensity defined as an average of the signal intensities prior to contrast agent injection. The other types of parameters are model-based parameters which are determined by applying a two-compartment model (Extended Workie’s model) describing the redistribution of contrast agent following a bolus injection, i.e. the contrast agent exchange between the central compartment (blood plasma) and the peripheral compartment (extravascular extracellular space, EES), and the elimination of the contrast agent from the central compartment. The obtained pharmacokinetic parameters include the amplitude ($A$, [a.u.]), the exchange rate constant ($k_{ep}$, [min$^{-1}$]) and the elimination factors [67]. The amplitude $A$ is proportional to the transfer rate from blood plasma to EES, whereas the exchange rate constant $k_{ep}$ is the transfer rate from EES to blood plasma. The model-based parameters for the ROIs were determined by using the MINPACK-1 method for fitting the measured data [1].

6.2.2 Data processing and statistical analysis

The pharmacokinetic parameters, taken as a mean of the three consecutive suburethral regions, were calculated for each subject. To reduce measurement errors, the initial values of the pharmacokinetic parameters were defined as the average of two baseline values. The percentage changes in pharmacokinetic parameters were determined from the initial values and the subsequent values at the end of the treatment (at week 12). Results for ST3 (at week 4) and ST4 (at week 8) are not shown. The reproducibility of the pharmacokinetic parameters was evaluated by paired Student’s t-Test of the two baseline studies. An unpaired Student’s t-Test was used to compare the parameters in the baselines as well as the parameters and percentage change in
the finasteride and control group. Statistical significance was defined as \( p < 0.05 \). All data was analyzed using SPSS statistical software (SPSS Inc., Chicago, IL).

6.3 Results

Of the 12 randomized subjects, 11 had satisfactory image quality for quantitative analysis of the prostatic suburethral regions. One subject in the control group experienced dramatic motion during the baseline MRI scans. This impeded prostatic suburethral ROI placement, resulting in the exclusion of the subject from this analysis. During the baseline scans there were no statistically significant differences between the two groups (the finasteride group and the control group) and between the two baselines (ST1 and ST2), regarding prostate volume and all pharmacokinetic parameters (MER, \( T_{\text{max}} \), \( A \), and \( k_{ep} \)) as shown in Table 6.1.

At the end of the treatment (ST5), the mean time to maximum signal enhancement, \( T_{\text{max}} \) (in [min]), in the suburethral portion of the prostate was significantly longer in subjects treated with finasteride compared with controls (2.04 ± 0.64 min versus 0.88 ± 0.34 min) \( (p < 0.01) \). Figure 6.3 demonstrates typical changes in the time-signal intensity curves from baseline (ST1) to ST5 of a subject from the finasteride group.

The amplitude \( A \) (in [a.u.]) and exchange rate constant \( k_{ep} \) (in \([\text{min}^{-1}]\)) decreased in the finasteride group at the end of the treatment (ST5) as well. The relative change in the prostatic suburethral pharmacokinetic parameter \( A \) for the finasteride treated group was -39% ± 36%, which is significantly different from the controls (+61% ± 80%) \( (p < 0.05) \). Similarly, the relative change in prostatic suburethral pharmacokinetic
Figure 6.3: The contrast-enhancement curves in prostatic suburethral ROIs demonstrating differences in characteristic patterns before and after the finasteride treatment. The magnitudes of $A$ and $k_{ep}$ show a decrease at the end of the treatment (ST5) compared to baseline ST1. The mean $T_{max}$ in ST1 was 1.35 min (1.62, 1.21, and 1.22 min for ROI#1, #2, and #3 respectively) and increased to 2.30 min in ST5 (2.82, 2.04, and 2.04 min for ROI#1, #2, and #3 respectively). The mean amplitude $A$ in ST1 was 11.51 (13.63, 10.97, and 9.93 for ROI#1, #2, and #3 respectively) and decreased to 4.11 in ST5 (3.94, 4.02, and 4.37 for ROI#1, #2, and #3 respectively). The mean exchange rate constant $k_{ep}$ in ST1 was 2.55 $min^{-1}$ (2.49, 2.51, and 2.66 $min^{-1}$ for ROI#1, #2, and #3 respectively) and decreased to 1.07 $min^{-1}$ in ST5 (0.89, 1.04, and 1.28 $min^{-1}$ for ROI#1, #2, and #3 respectively).
### Summary of baseline results

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<td>Suburethral $T_{max}$ ± SD (min)</td>
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<td>Suburethral $A$ ± SD</td>
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<td>Suburethral $T_{max}$ ± SD (min)</td>
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<td>Suburethral $A$ ± SD</td>
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<td>Suburethral $k_{ep}$ ± SD (min$^{-1}$)</td>
<td>2.91 ± 0.93</td>
<td>3.44 ± 1.67</td>
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Table 6.1: Summary of suburethral pharmacokinetic parameters in two baseline MR measurements.

Parameter $k_{ep}$ for the finasteride treated group was $-34\% \pm 44\%$, significantly lower than the controls ($+58\% \pm 55\%$) ($p < 0.05$).

No significant differences were found in pharmacokinetic parameter MER. The relative change in prostatic suburethral pharmacokinetic parameter MER of the finasteride treated group ($2\% \pm 13\%$) was not significantly different from that of controls ($1\% \pm 26\%$) ($p = 0.95$).
6.4 Discussions

TURP is one of the most common surgical procedures performed by urologists. Compared to minimally invasive techniques such as transurethral microwave hyperthermia (TUMT), transurethral needle ablation (TUNA), water-induced thermotherapy (WIT), and interstitial laser therapy, TURP continues to be the mainstay of therapy and the gold standard surgical technique [10]. During TURP, an instrument is inserted up the urethra to remove the section of the prostate that is blocking urine flow. The suburethral tissue in the prostate is highly vascularized, so it is a key factor in controlling prostatic bleeding during and after TURP. Hochberg [29] and Pareek [52] proved that finasteride significantly decreased the suburethral prostatic microvessel density. These investigators used histology on the section from the prostatic surgery for benign disease. In our dynamic images, the regions of interest were placed on the suburethral area in the caudal part of the prostate. This area is usually not removed during TURP, and may continue to affect the hematuria after surgery.

Our results showed that the subjects in the finasteride group revealed reduced microcirculation as expressed by the lower and slower contrast enhancement, as quantified by increased $T_{\text{max}}$ and decreased amplitude, $A$, and exchange rate constant, $k_{ep}$, in the prostatic suburethral area. Fast dynamic contrast-enhanced MRI with high spatial and temporal resolution enables quantification of early contrast enhancement characteristics and assessment of microcirculation parameters [33]. The underlying mechanisms inducing different time-signal intensity curves depend on tissue specific factors which include the density, perfusion, and permeability of the microvessels as well as the properties of extravascular space [34]. The semi-quantitative parameter $T_{\text{max}}$ reflects the speed of gadolinium-based enhancement during the wash-in phase.
and is a parameter of microvessel density and microcirculation. The amplitude $A$ is proportional to the degree of signal enhancement and physiologically is a parameter of tissue blood and permeability surface area product of capillaries. The exchange rate constant $k_{ep}$ describes the exchange from extravascular extracellular space to blood and depends on perfusion and vessel permeability [67]. Although the gold-standard of histopathology such as vessel density count is missing in this study, it is highly probable that the increase of $T_{\text{max}}$ and decrease of $A$ and $k_{ep}$ in the prostatic suburethral area are reflecting a decrease of microvessel density (MVD) and microcirculation mediated by the anti-angiogenic effects associated with decreased VEGF expression [52]. The observed finasteride-induced changes of the pharmacokinetic parameters match findings of other investigators, such as reduced MVD in prostatic suburethral area from histopathology [29, 52], reduced blood loss during TURP [13], and inhibited hematuria after surgery [31]. It is important to note that histopathological measurements of MVD alone may not be a sufficient indicator of angiogenic activity, because it may not reflect functional microvascular characteristics such as perfusion or vessel wall leakage [59]. The anti-angiogenic property also enables finasteride to be used as a prostate cancer treatment [65], whose efficiency can be non-invasively monitored by DCE-MRI providing important information about the relative change in microcirculation and respectively MVD [59].

Finasteride was found to be significant in controlling hematuria and reducing perioperative bleeding at TURP. The standard dosage of 5 mg/day was always used in the following studies, where the treatment duration for reducing bleeding varied and could be 2 weeks [17], 8~10 weeks [13], or 2~4 months [27] before TURP. The treatment duration for reducing hematuria associated BPH was even longer, for example 3
months [54], 1 year [21], or mean 38 months (range 3 to 86 months) [31]. What is the optimum dose and how long should the patients be treated [17]? A further question is whether it is possible to adjust dosage and treatment duration for different patients. DCE-MRI may serve as a feasible and efficient tool to help answer these questions. The pharmacokinetic parameters \( T_{\text{max}} \), \( A \) and \( k_{\text{ep}} \) as biomarkers can be used to classify different levels of microcirculation in the prostate and therefore will be a good tool to predict blood loss and hematuria during and after surgery. By non-invasively monitoring changes in prostatic microcirculation, DCE-MRI can help determine the optimal medication dosage and find the most appropriate treatment duration.

One limitation of our study is that the subjects were beagles. Because of the anatomical differences between the human and dog prostate, future studies need to evaluate the pharmacokinetic parameters in human prostatic suburethral area during treatment. While we assume no effect of anesthesia on prostatic blood flow, it is a requirement for animals and different from clinical examinations. Furthermore, the accuracy of the pharmacokinetic parameters may be influenced by the temporal resolution of DCE-MR imaging. The MR imaging on high magnetic field, such as 3 Tesla and 7 Tesla, may offer higher spatial and temporal resolution enabling a more accurate calculation of quantitative parameters.

In conclusion, dynamic contrast-enhanced MRI is capable of non-invasively assessing the changes in prostatic suburethral microcirculation induced by finasteride. The quantitative pharmacokinetic parameters show considerable promise for being important biomarkers in patient management and drug development of BPH drugs such as 5α-reductase inhibitors, by in-vivo monitoring the microvascular changes in
the pretreatment to reduce perioperative bleeding at transurethral resection of the prostate, and in the treatment of hematuria and prostate cancer.
CHAPTER 7

FUTURE WORK AND PRELIMINARY RESULTS

7.1 Introduction

It is thought that glandular proliferation plays a role in BPH in that it causes progressive hyperplastic enlargement. Presence of capsule transmits the pressure of tissue expansion to the urethra and leads to an increase in urethral resistance, thus linking organ volume with BPH disease etiology. It is for this reason that MRI measurement of organ volume and microcirculation is expected to provide diagnostic markers. Furthermore it is known that BPH drugs affect prostatic blood circulation. For example, 5α-reductase inhibitors can inhibit angiogenesis and decrease microvessel density in prostatic suburethral tissue, and α1-blockers can relax prostatic smooth muscle and relief obstruction. Measurement of vascularity and blood perfusion are therefore thought to help elucidate the involvement of vascular changes in BPH prevention, as well as help in early diagnosis and treatment follow-up of BPH.

With high field (≥ 3T) MRI of human prostate, dynamic contrast-enhanced MRI (DCE-MRI) is capable of quantifying and visualizing microvascular characteristics such as microvessel density and vascular permeability. The achievable diagnostic
imaging quality of the prostate in high field imaging can be assessed without an endorectal coil in order to eliminate discomfort as well as morphologic distortion of the prostate and its surrounding. We expect to differentiate among microcirculation in different zones and periurethral region in prostate based on optimized image acquisition, analysis and modeling of the contrast agent pharmacokinetics, and further postulate that such information will be valuable for the study of the process of benign prostatic hyperplasia (BPH), and provide a sensitive non-invasive biologic marker for evaluation of BPH drugs 5α-reductase inhibitors and α1-blockers.

7.2 Preliminary Results

7.2.1 Anatomical Imaging for Human Prostate High Field MRI

All MRI examinations were performed on a 3 Tesla clinical MRI system (Achieva, Philips Medical). Healthy male volunteers were in the supine position by using an 8-channel SENSE cardiac coil. High quality T1-weighted and T2-weighted images were optimized for imaging in the axial or coronal direction.

T1-weighted images were obtained by a Turbo Spin Echo (TSE) sequence (TR/TE = 469/10.5 ms; field of view = 150 × 150 mm²; matrix = 256 × 256 with in plane resolution 0.59 × 0.59 mm²; number of excitations = 3; 20 slices; 3.0-mm slice thickness; Gap between slices = 1 mm). The acquisition time is 4 minutes 52.9 seconds. A good overview of the prostate and surrounding tissues, such as bladder, rectum, fat and muscles, are displayed as Figure 7.1.

T2-weighted images were obtained by TSE sequence (TR/TE = 2500/150 ms; field of view = 150 × 150 mm²; matrix = 512 × 512 with in plane resolution 0.29 × 0.29 mm²; number of excitations = 3; 20 slices; 3.0-mm slice thickness, gap between
Figure 7.1: T1-weighted MR images in the axial by T1-weighted TSE sequence at 3 Tesla clinical MRI scanner. TR/TE = 469/10.5 ms; Acquired voxel = 0.59 × 0.74 × 3 mm³.
Figure 7.2: T2-weighted MR images in the axial direction by T1-weighted TSE sequence at 3 Tesla clinical MRI scanner. TR/TE = 2500/150 ms; Acquired voxel = 0.49 × 0.62 × 3 mm³.

slices = 0.3 mm). The acquisition time is 7 minutes 7.5 seconds. A good overview of the substructure of the prostate, such as central zone, peripheral zone, is displayed as Figure 7.2.

T2-weighted coronal images was also obtained by TSE sequence (TR/TE = 2500/150 ms; field of view = 150 × 150 mm²; matrix = 512 × 512 with in plane resolution 0.29 × 0.29 mm²; number of excitations = 3; 20 slices; 3.0-mm slice thickness). The
Figure 7.3: T2-weighted MR images in the coronal direction by T1-weighted TSE sequence at 3 Tesla clinical MRI scanner. TR/TE = 2500/150 ms; Acquired voxel = 0.49 × 0.62 × 3 mm³.

acquisition time is about 5 minutes. The images are displayed in Figure 7.3. The detailed scanning parameter setting are listed in 7.7.

The volumetric analysis, and planar measurement of diameters, was performed using the Medical Image Processing, Analysis, and Visualization (MIPAV software package) [41]. Figure 7.4 is a snapshot of the 3D display of the contour of the transition zone and the prostate from one volunteer. The diameter measurements are displayed in Figure 7.4. The organ segmentation were implemented for the bladder,
Figure 7.4: The 3-dimensional view of prostate contours from T2-weighted MR images at 3 Tesla clinical MRI scanner.

neurovascular bundle (NVB), rectum, and seminal vesicles. Figure 7.5 shows the 3D-modeling of the shape and relative position of segmented prostate substructure.

7.2.2 High Resolution MR Images at High Field

In order to obtain new isotropic resolution images, 3D imaging sequences were optimized for thin slices. High resolution T1-weighted images were obtained by T1W-3D-Turbo field echo (TFE) sequence (TR/TE = 9.3/4.4 ms; shot interval/TI = 3000/968 ms; field of view = 200 ×200 mm²; matrix = 512 × 512 with in plane resolution 0.39 × 0.39 mm² (0.78 × 1.00 mm² acquired); number of excitations = 1;
Figure 7.5: Non-endorectal coil based 3T High Field MR 3D modeling of prostate, and surrounding tissues of prostate.

Figure 7.6: The diameter measurement of the prostate from T2-weighted MR images at 3 Tesla clinical MRI scanner.
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Figure 7.7: The scanning parameters for MR imaging sequences at 3T.

90 slices; 0.5-mm slice thickness (interpolated, 1-mm acquired)). The T1-weighted high resolution images are shown in Figure 7.8.

High resolution T2-weighted images were obtained by T2W-3D-TSE-DRIVE sequence (TR/TE = 1000/90 ms; field of view = 200 × 200 mm²; matrix = 512 × 512 with in plane resolution 0.39 × 0.39 mm² (0.78 × 1.16 mm² acquired); number of excitations = 1; 90 slices; 0.5-mm slice thickness (interpolated, 1-mm acquired)), where DRIVE is DRIVen Equilibrium RF reset prepulse at the end of TSE echo train to accelerate the relaxation time and return to equilibrium of the Mz magnetization. The properties about DRIVE include that (1) shorter TR's are used shortening the total scan time and reducing flow void artifact; and (2) DRIVE provides T2w contrast with a higher fluid signal than TSE without DRIVE. Figure 7.9 are the images from one volunteer. The detailed scanning parameter setting are listed in 7.7.

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Figure 7.8: The high resolution T1-weighted MR images by T1-weighted 3D TFE sequence at 3 Tesla clinical MRI scanner. TR/TE = 9.3/4.4 ms; Acquired voxel = 0.78 × 1 × 1 mm³.
Figure 7.9: The high resolution T2-weighted MR images by T2-weighted 3D TSE-DRIVE sequence at 3 Tesla clinical MRI scanner. TR/TE = 1000/90 ms; Acquired voxel = 0.78 × 1.61 × 1 mm³.
7.2.3 DCE-MRI at High Field

In order to estimate the concentration of contrast agent in tissue, a phantom with known concentration was made to evaluate the signal-vs-Gd concentration behavior and to determine image acquisition parameters suitable for DCE-MRI. The phantom is composed of six 15 ml-sized tubes, filled with different concentration of gadobutrol (Gd-BT-DO3A, Gadovist; Schering AG, Berlin, Germany). The concentrations were 0 mM, 0.125 mM, 0.25 mM, 0.5 mM, 1.0 mM, and 2.0 mM. These 6 tubes were placed in a large cylindrical container filled with saline for phantom study. These tubes could also be glued in a row and placed between the volunteer and the SENSE coil.

The image sequence used for DCE-MRI was T1W-3D-TFE sequence, which is an inversion recovery (IR)-preparation with fast gradient echo sequence. The signal intensity is related to shot delay (TS), inversion preparation time (TI) and T1 of the tissue

$$SI \approx |1 + e^{-TS/T1} - 2e^{-TI/T1}|.$$  \hspace{1cm} (7.1)

The shot delay and preparation time affect the signal intensity from tissues with varying contrast agent concentration. A linear relationship between signal intensity and contrast agent concentration is desired. Shot delay of 400 ms was used for high temporal resolution in DCE-MRI. Preparation time of 68 ms, 100 ms, and 200 ms were applied to the phantom and compared to the simulation results. The image is shown in Figure 7.10 (TR/TE = 4.4/2.1 ms; TS/TI = 400/100 ms). The experiment data plot of signal intensity and contrast agent concentration is shown in Figure 7.11. By assuming T10 = 1100 ms, relaxivity $r_1 = 5 \text{ mmol}^{-1}\text{sec}^{-1}$, we calculated the simulation results, shown as Figure 7.12. The experimental data match the simulation
Figure 7.10: T1-weighted MR image of a phantom from 3 Tesla MR scanner with TR/TE of 4.4/2.1 ms and TS/TI of 400/100 ms.

results. The linear relationship between $S/S_0 - 1$ and contrast agent concentration works for TS/TI = 400/200 ms. This relationship was further proved by placing the phantom between the body and the SENSE coil (Figure 7.13). No endorectal coil was used.

In order to test the linear relationship for the tissues, we took the T1 value of the prostate (1600 ms), muscle (900 ms), fat (400 ms) at 3T [14]. We also assume the relaxivity $r_1$ may vary from 3.0 to 6.0 $mmol^{-1}sec^{-1}$, this range was supposed to cover the different tissues in the human body at different magnetic field. Since we can not directly measure the tissue relaxivity, the linearity works for this range may guarantee the linearity in real patient. When TS/TI equals 400/200 ms, the relationships are
Figure 7.11: The signal intensity vs contrast agent concentration at different inversion time TI.

Figure 7.12: The simulation results of the signal intensity vs contrast agent concentration at different inversion time TI.
Figure 7.13: The signal intensity vs contrast agent concentration from the phantom by placing between human body and the SENSE coil.
Figure 7.14: The simulation result of the signal intensity vs contrast agent concentration in different body tissue by assuming different T1 and relaxivity.

plotted in Figure 7.14. The linearity nearly holds for contrast agent concentration less than 2 mM.

The T1W-3D-TFE sequence (TS/TI = 400/200 ms; TR/TE = 3.4/1.86 ms; field of view = 200 × 200 mm²; matrix = 256 × 256 with in plane resolution 0.78 × 0.78 mm² (1.56 × 2.06 mm²); number of excitations = 1; 20 slices; 2.0-mm slice thickness) was applied to beagles in DCE-MRI. The injection volume of the Gd-based contrast agent was 4.4 ml with hand injection within 5 seconds. The regions of interest were placed on the dynamic images (Figure 7.15) and the plots of the signal intensity were
Figure 7.15: The placement of ROIs on prostate and other tissues from DCE-MRI of a beagle.

successfully fitted by a two-compartment model (Figure 7.16). In order to capture the wash-in phase, slow injection rate (0.2 ml/s) will be used for further imaging.

7.3 Histology

The possible correlation between pharmacokinetic parameters and microvessel density/VEGF expression could be investigated. Since the gold standard of histology gives microvessel density/VEGF expression, the best correlated pharmacokinetic parameter will be significantly correlated to microvessel density/VEGF expression.
Figure 7.16: The corresponding time-signal intensity curves of the ROIs in Figure 7.15.
The parameters, such as $A$, $K^{\text{trans}}$, $k_{\text{ep}}$, MER, area under curve (AUC) will be likely positively correlated to microcirculation. The parameters, such as $T_{\text{max}}$, will be likely negatively correlated to microcirculation. The best selected pharmacokinetic parameter will be used to track the microcirculation changes during the pharmacotherapy. For example, finasteride will lead to decreased microvessel density on prostatic suburethral area, while alfuzosin may increase microcirculation in bladder neck and prostatic musculature. These different effects could be systematically investigated.

7.4 Conclusions

High field MR scanner (3T and 7T) provides superior spatial resolution and high soft-tissue contrast of the prostate and surrounding tissues. The superb morphological delineation together with functional MRI’s capability to map prostate anatomy and physiology can serve as a tool in BPH diagnosis, treatment planning and pharmacotherapy monitoring. The objective is to develop high field MRI as a method for identification and quantification of prostatic disease and as a tool for assessment of novel treatment agents.
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