Dynamic contrast-enhanced MRI parameter as a potential predictor of subject response to benign prostatic hyperplasia pharmacotherapy

G. Jia[1], J. T. Heverhagen[1], H. Henry[1], H. Polzer[1], K. T. Baudendistel[1], H. von Tengg-Kobligk[1], A. L. Levine[2], T. J. Rosol[2], M. V. Knopp[1]

[1]Department of Radiology, The Ohio State University, Columbus, Ohio, United States, [2]Department of Veterinary Biosciences, The Ohio State University, Columbus, Ohio, United States

Introduction

Benign prostate hyperplasia (BPH) is a highly prevalent ailment in old men. Benign prostatic hyperplasia (BPH) is a hyperplastic process involving both the stromal and epithelial tissues of the prostate, which is characterized by progressive enlargement of the prostate gland resulting in obstruction of the flow of urine from the bladder. Pharmaceutical treatment of BPH consists mainly of α-blockers and 5α-reductase inhibitor, which can cause the relaxation of prostatic smooth muscle and the relief of obstruction or can result in the reduction of prostatic volume and the reversal of the BPH process respectively. One thing needs to be considered is that these drugs are not uniformly effective in patient response. The dose of finasteride for treatment of BPH is 5 mg daily for adults, and it is suggested that "you may have to take this medicine for at least 6 months to see the full effect", which means the patient has to spend money for the drug and the inconveniences of taking the medicine every day before finding out whether the drug is effective. If the drug does fail, this long time period might aggravate the patient suffering and delay the effective treatment of BPH. An ability to predict which patients can benefit best from certain treatment is crucial in solving this dilemma.

Material and methods

The study was prospectively designed within an interdisciplinary team and approved by the local animal care committee. The subjects of this 4-month study were comprised of twenty-four male beagle dogs (mean age ± SD: 4.4 ± 0.9 years, range 3 to 6 years, mean weight ± SD: 10.9 ± 3.0 kg, range 7 to 18 kg) with an initial palpated prostate diameter larger than 2 cm. Subjects were randomly allocated to three pharmaceutical treatment categories and one control category containing six beagles each: (1), a 5α-reductase inhibitor (finasteride, Merck & Co., Whitehouse Station, NJ) group, (2), a high dose (10 mg/kg/day) group of an experimental drug: 17β-hydroxysteroid dehydrogenases (17β-HSD) inhibitor (SCH 488900, Schering-Plough Co., Kenilworth, NJ), (3), a low dose (3 mg/kg/day) group of the 17β-HSD inhibitor, (4), a placebo group receiving vehicle only. Investigators were blinded as to group placement schedule until after all subjects had completed this study. The subjects were scanned 5 times by MRI: the first baseline (Study #1) was carried out 3 weeks prior to treatment, and the second baseline (Study #2) was immediately prior to the initiation of treatment; 3 follow-ups during-treatment were performed at 4 weeks (Study #3), 8 weeks (Study #4), and 12 weeks (Study #5) after the start of the treatment. Conventional axial MR images covering the whole prostate were obtained for prostate volume measurements. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) was performed with a 3D-SPGR sequence by constant-rate intravenous infusion of Gadoteridol (Prohance[TM], Bracco Diagnostic Inc. Princeton, NJ). The time-intensity curves of parenchymal and periurethral regions of interest (ROIs) (Fig. 1) obtained from DCE-MRI were analyzed, and the microcirculation characteristics were assessed by using non-model-based parameters (the maximum signal ratio S_{max}/S_0, the time to maximum signal enhancement T_{max}) and two-compartment-model-based parameters (the amplitude of contrast enhancement A, the exchange rate k_{ep} and the elimination factor k_{el}) by using an in-house developed software based on IDL (Interactive Data Language, v. 6.0, Research Systems, Boulder, CO).

Image postprocessing included prostate volume segmentation and DCE-MRI analysis. The prostate volume segmentation was completed using the MIPAV software package by a semi-automated method by comparison of T1-weighted images and T2-weighted images. The baseline values of the parameters were defined as the average of the parameters in Study #1 and #2. The relative prostate volume reduction was defined as the difference between the baseline prostate volumes and during-treatment volume divided by the baseline volumes. The baseline parameters were tested for the possibility of predicting the relative prostate volume reduction. All data was analyzed using SPSS statistical software (SPSS Inc., Chicago, IL). The difference of the prostate volume and parenchymal maximum signal ratio between two baselines was tested using a paired-samples t-test where there is no significant difference if P > 0.05. The linear relationship between the parameters in the baselines and the linear relationship between the baseline parameters and prostate volume reductions were tested using the Pearson linear correlation coefficient r (two-tailed test), where statistical significance was defined as P < 0.05.

Results

The relative prostate volume reductions before and during the treatment were plotted according to different treatment groups (Fig. 2). In the control group, there were basically no volume changes; in the low dose experimental drug group, two-thirds (4/6) of the subjects had volume reduction with relative prostate volume reduction between 16% and 58%; in the high dose experimental drug group, all six subjects had volume reduction with relative prostate volume reduction ranging from 8% and 70%; in the finasteride group, all subjects had volume reduction with relative prostate volume reduction between 32% and 66%.

The parenchymal S_{max}/S_0 is significantly correlated to relative volume reduction at the end of the trial for all three pharmaceutical treatment groups. No meaningful significant correlation was recognized between the relative prostate volume reduction and the following parameters: baseline prostate volume, all periurethral DCE-MRI parameters, parenchymal T_{max}, k_{ep}, and k_{el}. The linear relationships between baseline parenchymal S_{max}/S_0 and the relative prostate volume reduction in Study #5 in three treatment groups provide following parameters: the slope of the fitting line is -1.51 for low dose experimental drug group, -0.52 for high dose experimental drug group, -0.45 for finasteride group. The intercept of the fitting line is 5.10 for low dose experimental drug group, 2.15 for high dose experimental drug group, 2.02 for finasteride group. Within the treatment group, subjects with smaller parenchymal maximum signal ratio had larger relative prostate volume reduction.

Discussion and conclusion

In the three drug groups we found a linear correlation between relative prostate volume reduction and the baseline parenchymal maximum signal ratio S_{max}/S_0, in which the negative correlation means that the subject with a smaller parenchymal S_{max}/S_0 will a higher relative prostate volume reduction. How to explain the linear relationship between baseline parenchymal DCE-MRI parameter maximum signal ratio and relative prostate volume reduction? The answer can be speculated from drug-induced apoptosis and intraprostatic pressure. An increase in the number and size of the glands and ducts in BPH may increase the pressure inside the prostate and the compressive force among the tissue cells is prominent to push the capsule out resulting more round shape of the prostate. As the pharmacotherapy treatment causes the apoptosis of the epithelial cells, the intraprostatic pressure may decrease, which may leads to the destruction of the force balance among the surgical capsule, prostatic urethra, and hyerplastic prostate gland. The tensile strength of the prostatic capsule may compress the prostate and cause the decrease of the prostate volume until it reaches a new force balance. Furthermore, the intraprostatic compressive pressure could be related to the parenchymal maximum signal ratio S_{max}/S_0 because the mechanical pressure may constrict interstitial space and the DCE-MRI parameter S_{max}/S_0 was found to positively correlate to the vascular density and interstitial water space. So the **A**poptosis **P**ressure-**I**nduced **Vo**lume **R**eduction (APIVOR) model has been proposed to quantitatively explain the linear relationship.

In conclusion, the ability to pre-select patients who would benefit most from BPH pharmacotherapy and to exclude the patients who might not benefit may exist and appears explainable. As evidenced through the APIVOR model, our investigations reveal that the parenchymal maximum signal ratio in DCE-MRI has a significant linear relationship to the relative prostate volume reduction after a three month drug trial. Future efforts should be concentrated on evaluating the APIVOR model in clinical trials and applying it to routine clinical practice.

References
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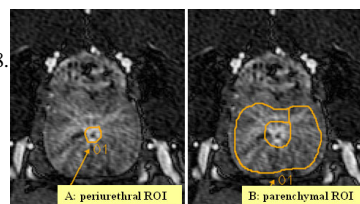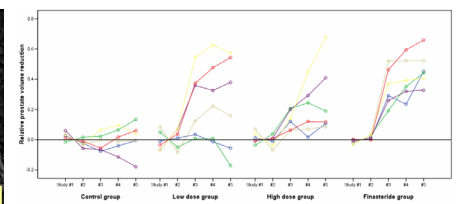5. Jia G, et al. RSNA 2003 Abstract Code 1243.

Figure 1

Figure 2