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Effect of intravascular contrast agent on diffusion and perfusion fraction coefficients in the peripheral zone and prostate cancer

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A R T I C L E I N F O

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A B S T R A C T

Purpose: To determine whether water diffusion and the perfusion fraction coefficients in prostate peripheral zone (PZ) and prostate cancer (PCa) are affected by intravenous contrast injection and explore the potential mechanism behind previously reported differences between pre- and post-contrast ADC values.
Methods: Our institutional review board waived informed consent for this HIPAA-compliant, retrospective study, which included 32 patients (median age, 63 years; range, 47–77 years) with biopsy-proven, untreated PCa who underwent 3-Tesla MRI, including DW-MRI at b-values 0, 400, 700, 1000 s/mm^2 before and after gadolinium injection. For regions of interest (ROIs) in presumed benign PZ and PZ PCa, apparent diffusion coefficient (ADC), perfusion fraction f, and diffusion coefficient D were estimated voxel-wise, and signal-to-noise ratio (SNR) and contrast-to-noise (CNR) were estimated. Pre- and post-contrast measurements were compared by Wilcoxon signed-rank test; $P < 0.05$ was considered significant.
Results: In PZ, f ($P = 0.002$) was significantly higher on post-contrast imaging than on pre-contrast imaging, but ADC and D values did not change significantly ($P = 0.562$ and 0.295 respectively). In PCa, all parameters differed significantly between post-contrast and pre-contrast imaging ($P < 0.0001$ for ADC, $P = 0.0084$ for D, and $P = 0.029$ for f). On post-contrast imaging, SNR was not significantly different in PZ ($P = 0.260$) but was significantly lower in PCa ($P < 0.0001$); CNR did not change significantly ($P = 0.059$).
Conclusion: After contrast injection, ADC and D declined significantly in PCa only, while f increased significantly in both PCa and PZ. Pre- and post-contrast diffusion parameters cannot be used interchangeably for diagnostic purposes that require quantitative diffusion estimates.

1. Introduction

Multi-parametric magnetic resonance imaging (mp-MRI) of the prostate is increasingly being used in the detection, localization, staging, risk stratification and surveillance of untreated prostate cancer, as well as for guiding biopsies and interventions and assessing potential cancer recurrence [1]. In addition to T_1- and T_2-weighted anatomic MRI sequences, mp-MRI examinations incorporate one or more sequences that assess function or physiology—typically, dynamic contrast-enhanced MRI, which reflects vascularity and perfusion; diffusion-weighted imaging (DWI), which reflects restriction of water diffusion and thus corresponds to properties such as cellular density, membrane permeability and spacing between cells [2]; and/or, more rarely, proton MR spectroscopic imaging (MRSI), which shows changes in relative metabolite levels that occur in prostate cancer [3].

Typically, DWI is obtained before the administration of any intravenous contrast agents. A number of studies have examined the effects of contrast injection on DWI in these circumstances in, for example, the brain [4], breast [5–7], and abdominal organs such as the liver, spleen, or pancreas [8]. The results have been conflicting. Some studies have found that the injection of contrast does not significantly change ADC values for tumors [7], whereas others have found significant changes in ADC values [4,5,9–11]. Furthermore, the mechanism by which contrast medium alters diffusion measurements is not well understood. Some investigators have suggested that the changes are primarily due to T2* effects [12,13], while others have proposed that the measured decrease in ADC values is due to the suppression of the effect of microperfusion on DWI signal [5].

Studies in the prostate, specifically, have yielded no consensus on the effects of contrast medium on diffusion measurements in normal tissue of the peripheral zone (PZ) or in prostate cancer (PCa) in the PZ; nor is there any consensus on its effects on the detection of PCa in the PZ by DWI. Liu et al. reported significantly lower ADC values in tumor regions on post-contrast as opposed to pre-contrast DWI but found no

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Table 1
Comparison of median (± standard deviation) estimated parameters from regions-of-interest in peripheral zone tissue thought to be benign and in prostate cancer. The asterisk indicates significance (Wilcoxon rank-sum test *P*-value < 0.05). All values were estimated using all four b-values.

	Peripheral zone				Prostate cancer			
	Pre-contrast	Post-contrast	Difference	*P* value	Pre-contrast	Post-contrast	Difference	*P* value
ADC [$\times 10^{-3}$ mm^2/s]	1.60 ± 0.30	1.61 ± 0.30	0.015 ± 0.17	0.562	1.27 ± 0.26	1.12 ± 0.27	−0.092 ± 0.13	< 0.001*
D [$\times 10^{-3}$ mm^2/s]	1.27 ± 0.33	1.23 ± 0.28	−0.028 ± 0.19	0.295	0.94 ± 0.25	0.87 ± 0.25	−0.085 ± 0.16	0.0084*
f	0.25 ± 0.08	0.28 ± 0.07	0.025 ± 0.045	0.002*	0.24 ± 0.07	0.25 ± 0.08	0.015 ± 0.036	0.029*

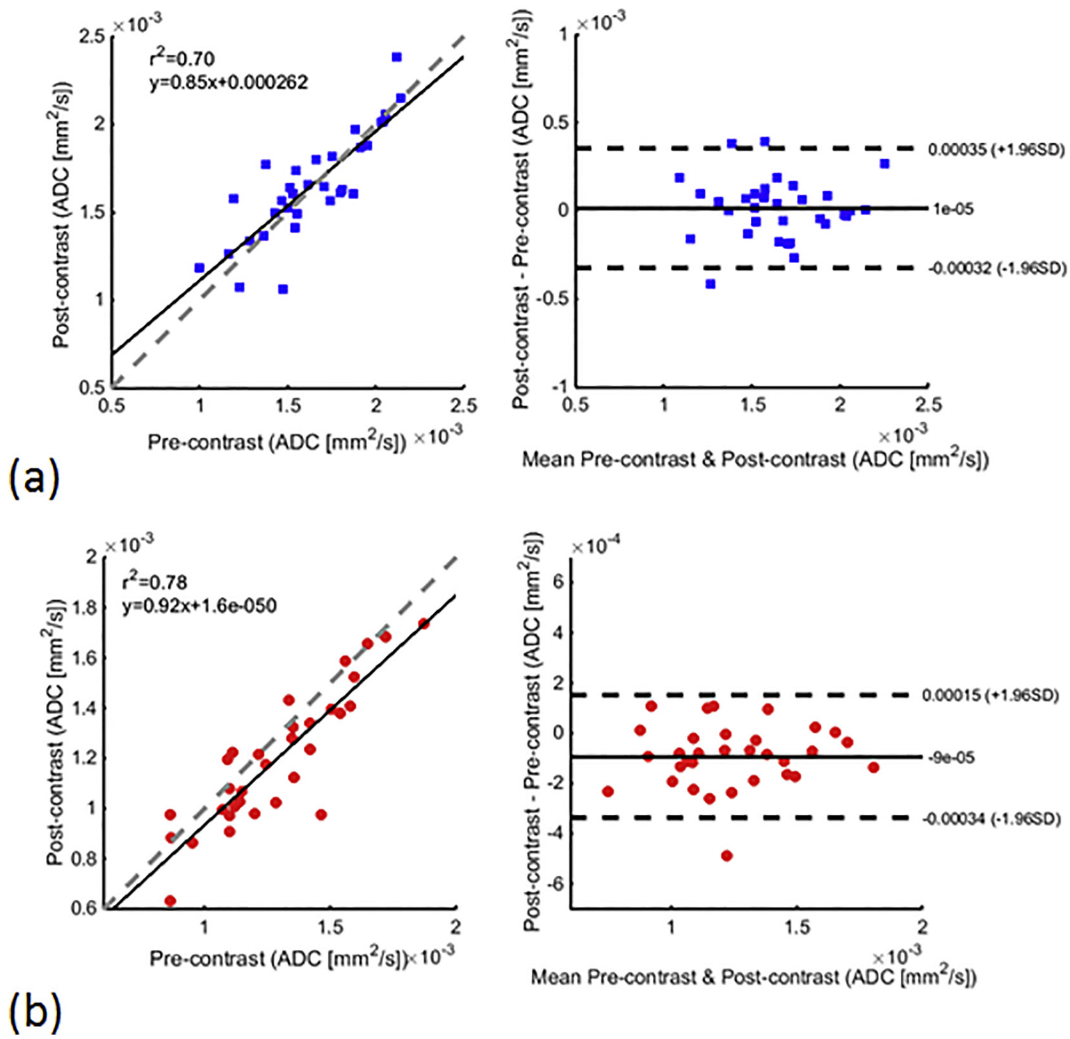

Fig. 1. Scatterplots and Bland-Altman plots of mean ADC values for regions-of-interest in (A) peripheral zone tissue thought to be benign and (B) prostate cancer. The correlation between pre-contrast ADC and post-contrast ADC ($r^2 = 0.70$ and $r^2 = 0.78$, respectively) was significant ($P < 0.001$ for both).

significant differences between post- and pre-contrast ADC values in normal prostate tissue [9]. Kim et al. evaluated ADC, exponential ADC, signal-to-noise ratio (SNR), and contrast-to-noise ratio (CNR) values measured from pre- and post-contrast DWI in prostate cancer and in PZ of the prostate and found no significant differences [14].

In the investigation of DWI described here, we took a systematic approach aimed at identifying a mechanism that might explain the existence of significant differences in pre- and post-contrast diffusion and perfusion parameters—as well as the absence of such differences in some cases. In addition to measuring ADC values before and after contrast injection, we extended the mono-exponential model to incorporate the contribution of pseudo-perfusion to the signal intensity and evaluated the impact of contrast injection on molecular diffusion (*D*) and perfusion fraction (*f*). Our goals were to determine whether diffusion or perfusion parameters are affected by contrast medium in patients with prostate cancer and to evaluate if parameters estimated after contrast injection can be interchangeably used and compared with pre-contrast DWI parameters for clinical evaluation of prostate cancer.

2. Material and methods

2.1. Patient population

Our institutional review board waived the requirement for informed consent for this retrospective study, which was compliant with the Health Insurance Portability and Accountability Act. A total of thirty-two patients were identified (median age, 63 years; range, 47–77 years) who met the inclusion criteria for our study, which were as follows: 1)