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Original Research

Time Course Study on the Effects of Iodinated Contrast Medium on Intrarenal Water Transport Function Using Diffusion-Weighted MRI*

Jing Wang, PhD,[1] Yudong Zhang, PhD,[2] Xuedong Yang, PhD,[2] Xiaoying Wang, MD,[1,2*] Jue Zhang, PhD,[1,3*] Jing Fang, PhD,[1,3] and Xuexiang Jiang, MD[2]

Purpose: To assess the effects of intravenous-injected iodinated contrast medium (CM) on intrarenal water diffusion using noninvasive diffusion-weighted MRI (DW-MRI).

Materials and Methods: Ten New Zealand White rabbits were randomized to receive a 6 mL/kg body weight intravenous injection of clinically used iopamidol-370 (n = 7) or an equivalent amount of 0.9% physiological saline (n = 3). A sequential DW-MRI was performed to estimate the intrarenal apparent diffusion coefficient (ADC) at 24 h before and 1 h, 24 h, 48 h, and 72 h after administration.

Results: Iopamidol produced a progressive ADC reduction in inner stripes of the renal outer medulla (IS) by 13.92% ($P = 0.05$) at 1 h, 17.52% ($P = 0.02$) at 24 h, 20.23% ($P = 0.01$) at 48 h and 16.31% ($P = 0.04$) at 72 h after injection. Cortical ADC was decreased by 14.14% ($P = 0.01$) at 48 h and 14.12% ($P = 0.01$) at 72 h after injection. Iopamidol produced slight decrease of ADCs in outer stripes of the outer medulla (OS) and inner medulla (IM) of kidney but without statistical difference. In control group, no significant ADC changes was observed in each anatomic compartment due to saline injection ($P > 0.05$).

Conclusion: As demonstrated by DW-MRI, intravenous iopamidol injection resulted in a successive reduction of intrarenal water diffusion, particularly in IS of kidney. This MR technique may be used as a noninvasive tool to perform a time course study of the pathogenesis associated with contrast-induced nephropathy (CIN).

Key Words: MRI; kidney; diffusion-weighted imaging; contrast-induced nephropathy
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CONTRAST-INDUCED NEPHROPATHY (CIN) is a common iatrogenic event following intravascular injection of iodinated contrast medium (CM) (1–4). With increased usage of iodinated CM during radiological or interventional procedures, CIN has become one of the most prevalent causes of acute renal failure (ARF), especially in patients suffering from diabetes or cardiovascular pathology (5–7). The pathogenesis of CIN, however, is currently unclear (8)

Previous research has used invasive laser-Doppler probe or Clark-type microelectrodes to demonstrate that the renal ischemia and anoxia plays an important role in the development of CIN (9). To date, a noninvasive technique for the investigation of functional alterations within the kidney has not been well established. Diffusion-weighted MR imaging (DW-MRI) is a technology in which the contrast between tissues depends primarily on the Brownian motion of water molecules. The image contrast of DW-MRI is different from conventional MR techniques that allows to the observation of functional alteration in normal or abnormal structure of tissues (10). Moreover, the water diffusion between intra and extra-cellular can be estimated by the apparent diffusion coefficient (ADC) (11). In renal parenchyma, the value of ADC mainly depends on the intra- and extra-cellular components fraction, ambient temperature, membrane permeability and capillary perfusion (12–14). Thus, DW-MRI can quantify alterations in water content as well as water exchange rate between intra and extra-cellular aspects of the kidney.

Accordingly, this study aimed to quantify the intrarenal water diffusion responses to iodinated CM injection, as compared to a placebo, in 10 healthy rabbits using a spin-echo & echo planar imaging (SE-EPI) DW-MRI technique. We hypothesized that this technique would be sensitive to changes in intrarenal water diffusion following iodinated CM injection, and more specifically, that the CM injection would result in a longer time course (>1 h) decrease in ADC values throughout the kidney. As such, this MR technique may be used as a noninvasive tool to study the pathogenesis associated with CIN.

[1]Academy for Advanced Interdisciplinary Studies, Peking University, Beijing, China.
[2]Department of Radiology, Peking University First Hospital, Beijing, China.
[3]College of Engineering, Peking University, Beijing, China.
J.W. and Y.Z. contributed equally to this work.
*Address reprint requests to: X.W., Department of Radiology, Peking University First Hospital, No. 8, Xishiku Street, Xicheng District, Beijing, China, 100034. E-mail: cjr.wangxiaoying@vip.163.com or J.Z., Academy for Advanced Interdisciplinary Studies, Peking University, Yiheyuan Road No. 5, Beijing, China, 100871. E-mail: zhangjue@pku.edu.cn
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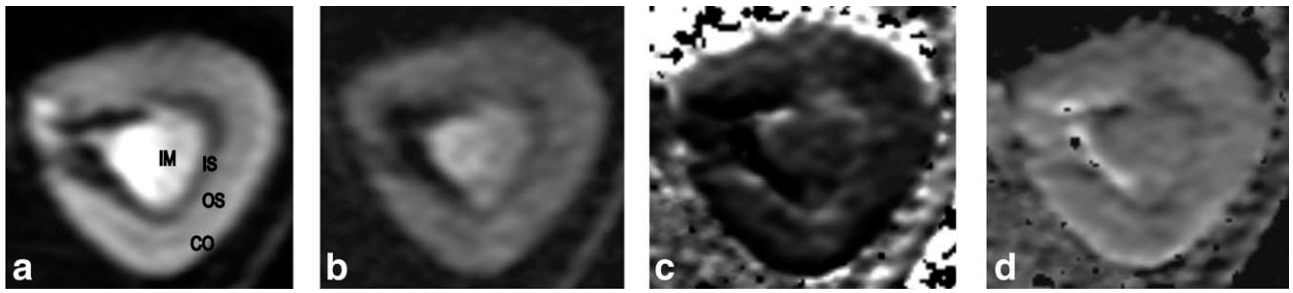

Figure 1. Axial DW-MRI images (2300/70 ms; flip angle, 90°) and ADC measurements in a left kidney. **a**: The DW image (b = 0 s/mm^2) obtained in 128×128 matrix with FOV of 8.0 cm provided enough spatial resolution to distinguish four anatomic compartments: the cortex (CO), the outer stripes of the outer medulla (OS), the inner stripes of the outer medulla (IS) and the inner medulla (IM) of kidney. **b**: DW image obtained at b = 800 s/mm^2. **c**: The exponential ADC map. **d**: The corresponding ADC map.

MATERIALS AND METHODS

Animals and MR Examination

This study was approved by the university animal care and use committee. Ten male New Zealand white rabbits (body mass ranged from 2.5–3.0 kg) were examined. The rabbits were given free access to standard feed and tap water until the day of experiment. They were anaesthetized with 5% pentobarbital sodium (dosage = 0.5 mL/kg body mass) by means of a venous cannula (24G) inserted into the marginal ear vein. During MR examination, the rabbit was placed in a supine position and the abdomen was firmly bound with a tourniquet to limit motion of kidney.

Experiments were conducted in a 3.0 Tesla (T) whole-body MR scanner (Signa Excite^{TM}; GE Medical Systems, Milwaukee, WI) with a commercial QUAD-KNEE coil. A coronal plane through the center of both kidneys was determined for scout images. The following sequences were then collected on each rabbit during a single MR session: (a) T2-weighted fast spin-echo (repetition time [TR] = 4000 ms, echo time [TE] = 105 ms, flip angle = 90°, bandwidth = 62.5 kHz, the number of excitations(NEX) = 3, 5 mm-thick, axial slices with a 256 × 224 matrix and 12 × 12 cm^2 field of view [FOV]); (b) SE-echo echo-planar imaging (TR = 2300 ms, TE = 70 ms; flip angle = 90°, bandwidth = 250 kHz, NEX = 2, 5 mm-thick, axial slices with a 128 × 128 matrix and 8 × 8 cm^2 FOV; Diffusion sensitizing gradient was applied on three directions, b factors of 0 and 800 s/mm^2). As the tourniquet bound to the upper abdomen to limit the motion of kidney mostly leaded to a marked shift of right kidney to the thoracic cavity, which make the images unacceptable due to respiratory movement, thus, for each rabbit, only the images of left kidney was recorded for the DW-MR examination.

The rabbits were randomized into an experimental group (EG, n = 7) or a control group (CG, n = 3). The DW-MR images were obtained before iodinated CM injection as a baseline scan. After a 24-h control period, rabbits within the EG received an intravenous injection of a nonionic hyper-osmolar iodinated CM, Iopamidol-370 (Isovue, 370 mg I per milliliter, 796 mOsm/kg H_2O, Bracco Diagnostics Inc.) with dosage of 6 mL/kg body weight. Rabbits within the CG were given an equivalent amount of 0.9% physiological saline. Then DW-MR examination was performed at 1 h, 24 h, 48 h, and 72 h following injection to perform the time course evaluation of ADC changes within the renal parenchyma.

Postprocessing

ADC maps were constructed with FUNCTOOL software on the Advanced Workstation 4.2 (GE Medical Systems) by fitting the signal intensity values to a mono-exponential model, as described in Eq. 1:

$$ADC = \frac{\ln S_2 - \ln S_1}{b_2 - b_1} \quad [1]$$

Here, S_2 is the signal intensity when b = 800 s/mm^2, and S_1 is the signal intensity when b = 0 s/mm^2. To minimize the effects of magnetic field inhomogeneities or motion-related artifacts, a manual analysis was performed at each slice and data with motion or field inhomogeneity-related artifacts were discarded. Based on the anatomic images, each ROI covering 20–30 mm^2 area was respectively drawn in cortex (CO), outer stripes of the outer medulla (OS), inner stripes of the outer medulla (IS), and inner medulla (IM) to obtain quantitative estimates of ADC, as shown in Figure 1.

Statistical Analyses

All results are reported as mean ± standard deviation (SD). ADC values obtained in the CO, OS, IS, and IM were grouped into "baseline," "1 h," "24 h," "48 h," and "72 h," respectively. Then, a one-way analysis of variance (ANOVA) and Fisher's least significant difference (LSD) test were performed to test the intrarenal water diffusion in response to iopamidol stimulation between different groups.

RESULTS

One EG rabbit died 24 h following intravascular administration of iodinated contrast agents. Data from this rabbit were discarded. The other nine rabbits successfully completed the entire protocol. The DW images obtained for each of these rabbits contained sufficient spatial resolution and signal-to-noise

Table 1
Baseline Apparent Diffusion Coefficient Values

Groups	N	ADC $\times 10^{-3}$ mm^2/s			
		CO	OS	IS	IM
EG	6	2.03 ± 0.24	1.85 ± 0.22	1.73 ± 0.25	1.77 ± 0.20
CG	3	2.05 ± 0.13	1.86 ± 0.10	1.67 ± 0.14	1.73 ± 0.13

Values are mean ± SD.

ratio (SNR) to clearly outline the cortical and medullary regions in global kidney, and thus, reliable ADC values could be estimated.

Table 1 showed the baseline ADCs in CO, OS, IS, and IM were similar in EG and CG (Independent Samples t-test, $P > 0.05$), the statistical difference was tested between these renal compartments in both groups (ANOVA, $P < 0.05$). Time course DW images following injection showed differences between the two groups (Table 2). In EG, a significant reduction in water diffusion in IS ($P < 0.05$) was observed at 1 h, aggravated and lasted until 48 h, while only slightly alleviated at 72 h (Fig. 2a). A slight decrease in cortical diffusion was found at 1–24 h ($P > 0.05$), but a prominent reduction was observed at 48–72 h ($P < 0.05$). The ADCs in OS and IM were slightly reduced without statistical differences. Iopamidol produced progressive decrease of ADC in IS induced by proximate 13.92–20.23% of the baseline values from 1 to 48 h after injection. The ADC declines occurred in CO, OS and IM were less than IS.

The time course of renal ADCs changes following the saline injection in control group was shown in Table 3. Postinjection scans demonstrated that no significantly statistical changes in ADC were observed at each time point in all of the four anatomic compartments (Fig. 2b).

Figure 3 illustrates a time course effect of iopamidol on renal diffusion within the different anatomic compartments. In EG group, a significant decrease in ADC was observed at 1 h after injection, particularly in IS of kidney. This CM-induced diffusion deficiency was aggravated within 24–48 h and alleviated within 72 h.

DISCUSSION

Our experiments have demonstrated that it is feasible to monitor the time course effects of iodinated CM on the renal function in rabbit model using a sequential DW-MRI. Although DW-MRI is already routinely used and is valuable for the detection of acute vascular lesions in patients with stroke symptoms, its application in abdominal organs is challenging due to respiration, peristalsis and magnetic susceptibility artifacts (15,16). Only in recent years it reveals an appreciable progress in DW-MRI of the kidneys (13,17,18), but to the best of our knowledge, little work has been done to evaluate the renal function sequentially under the insult produced by radiographic contrast agents using a noninvasive DW-MR technique. In this study, as with available preparation to limit the respiratory movements, the DW-MR images were almost free of motion artifacts. By using a relatively small FOV on 3.0T MR scanner to increase the spatial resolution and reduce susceptibility artifacts, each rabbit's images have sufficient spatial resolution and SNR to accurately outline the renal cortical and medullary regions (CO, OS, IS, and IM) and subsequently quantify ADC values within these regions.

The results of this study indicated that the hyperosmotic iopamidol certainly produced a progressive reduction in intrarenal diffusion, particularly in IS of kidney. Our results are partially supported by a previous report by Laissy et al (19). In their study, a dynamic serial DW-MRI was performed to monitor the effects of isosmotic iodixanol on the renal function based on a rat model. The rat DW-MRI experiments revealed a significant decrease in renal diffusion at 12 min after the iodixanol injection, which lasted at least until 24 minutes. They found an approximate 15% decrease in ADC of the whole kidney induced by the iodixanol at 24 min after injection. Their study also indicated that the ADC declines occurred earlier for the cortex and lasted for a shorter time than the medulla. Similar results were obtained in our study. In the experimental group, iopamidol produced prominent reduction in cortical ADCs by the first hour after iopamidol injection, and a persistent decrease in cortical ADCs was observed for 72 h. With regard to medullar ADCs, we compared ADCs in the kidney of OS, IS, and IM, which have been measured more accurately than the study of Laissy et al based on the higher field strength and improved MR protocols. The

Table 2
Time Course ADC Changes in Different Compartments in Response to Iopamidol Injection

Time course	ADC $\times 10^{-3}$ mm^2/s (N=6)			
	CO	OS	IS	IM
Baseline	2.03 ± 0.24	1.85 ± 0.22	1.73 ± 0.25	1.77 ± 0.20
Post-1h	1.95 ± 0.21	1.79 ± 0.17	1.41 ± 0.17	1.67 ± 0.19
Post-24h	1.88 ± 0.16	1.67 ± 0.22	1.36 ± 0.13*	1.65 ± 0.24
Post-48h	1.78 ± 0.19*	1.60 ± 0.27	1.33 ± 0.25*	1.57 ± 0.22
Post-72h	1.78 ± 0.16*	1.64 ± 0.28	1.39 ± 0.21*	1.63 ± 0.14

*Fisher's least significant difference-test with baseline value of ADC, $P < 0.05$.

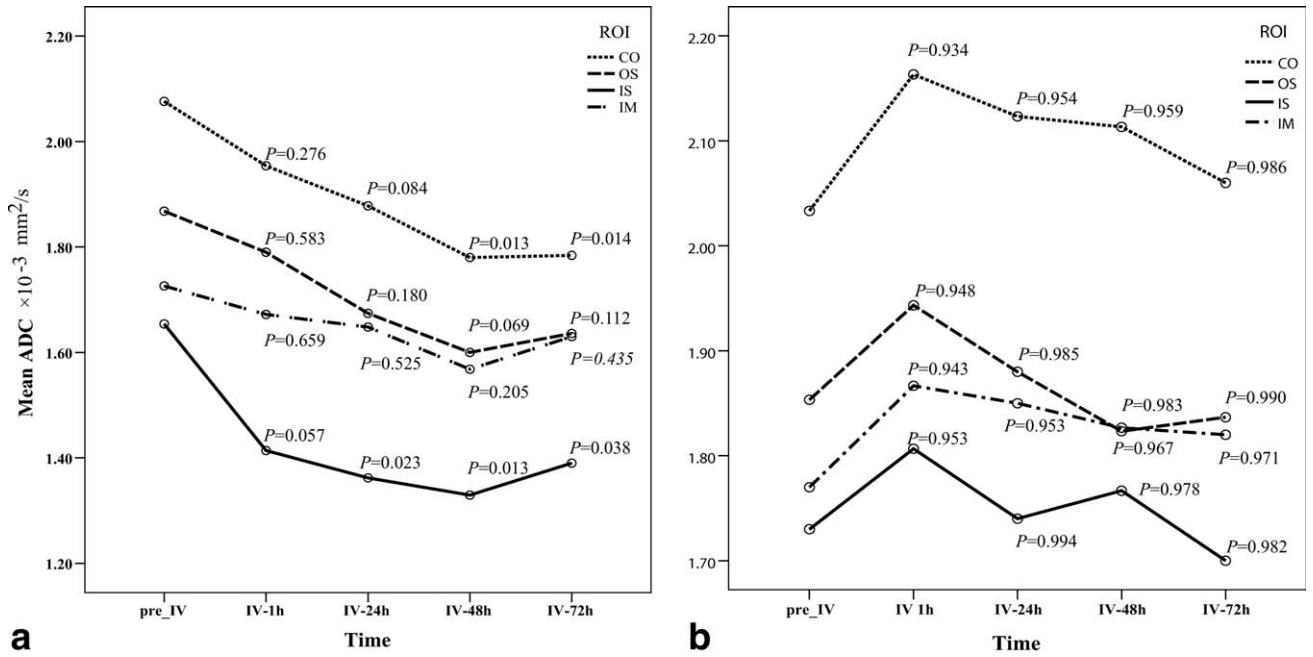

Figure 2. Sequential ADC changes following administration of iopamidol and saline injection in different renal compartments. **a**: A progressive reduction in intrarenal ADC was observed by the first h after iopamidol injection, lasted and aggravated until 24–48 h. This CM induced reduction in diffusion mildly alleviated by 72 h after injection. The prominent diffusion deficiency was found in CO and IS, but not in CO, OS or OM. **b**: Saline did not produce any statistically significant alteration in each renal compartment. Note: y-axis scales in graph (a) ranged from 1.2 to 2.2 $\times 10^{-3}$ mm^2/s with a 0.2 $\times 10^{-3}$ mm^2/s increment; y-axis scales in graph (b) ranged from 1.7 to 2.2 $\times 10^{-3}$ mm^2/s with a 0.1 $\times 10^{-3}$ mm^2/s increment. The *P*-values are a comparison relative to the baseline for the particular region of interest.

comparison indicated that the IS was more vulnerable to the action of iopamidol than OS or IM. The early ADC response to iodinated CM is primarily due to sustained vasoconstriction, which is confirmed by Laissy et al and our study, for the ADC values in both studies decreased in a similar way to renal blood flow after injection, as previously shown with laser flowmetry (20). But the intra-renal hemodynamics is not the only mechanism acting on diffusion. Blood flow in the cortex is approximately 10-fold greater than that in medulla, while a higher ADCs in the medulla compared with the cortex were observed in some previous studies (21). In addition, a short-term response of hemodynamics to the iodinated CM has been reported in most literatures (22–24), while a progressive decrease in renal ADCs that lasted up to 72 h after iopamidol injection was observed in our experiments. The 5-day time course study indicated that the renal ADCs reduction is associated not only with the blood perfusion but also with the water diffusion. Kidney hemodynamics could be partially appreciated by the ADC measurement only when small b-value is used in DW-MRI, while the contributions from capillary perfusion and tubular flow on DW-MR images can be diminished with an increased b-value (25). Despite that the kidneys receive approximately 25% of the cardiac output, which represents perfusion of more than 400 mL/100 g/min, the signals in DW-MR images may largely dependent on intrarenal water contents, especially under high b-value. Thus it was concluded that the early response of renal ADCs to the iopamidol injection was primarily due to a short-term vasoconstriction of renal vascular system, while the delayed decrease in renal ADCs, particularly in the kidney of IS, mainly depended on the limitation of water diffusion.

The advantage of our study is using a 5-day observation using DW-MRI to consecutively monitor the sequential diffusion characteristics in rabbit kidney. This experimental method allows for investigating the progressive renal insufficiency in the following 72 h due to iopamidol administration. Results from the

Table 3
Time Course ADC Changes in Different Compartments in Response to Saline Injection

	ADC $\times 10^{-3}$ mm^2/s (*N*=3)			
Time course	CO	OS	IS	IM
Baseline	1.73±0.24	1.57±0.22	1.59±0.25	1.52±0.20
Post-1h	1.86±0.11	1.66±0.19	1.67±0.18	1.62±0.08
Post-24h	1.82±0.12	1.60±0.08	1.60±0.06	1.60±0.03
Post-48h	1.81±0.09	1.54±0.10	1.63±0.04	1.58±0.12
Post-72h	1.76±0.17	1.56±0.09	1.56±0.06	1.57±0.05

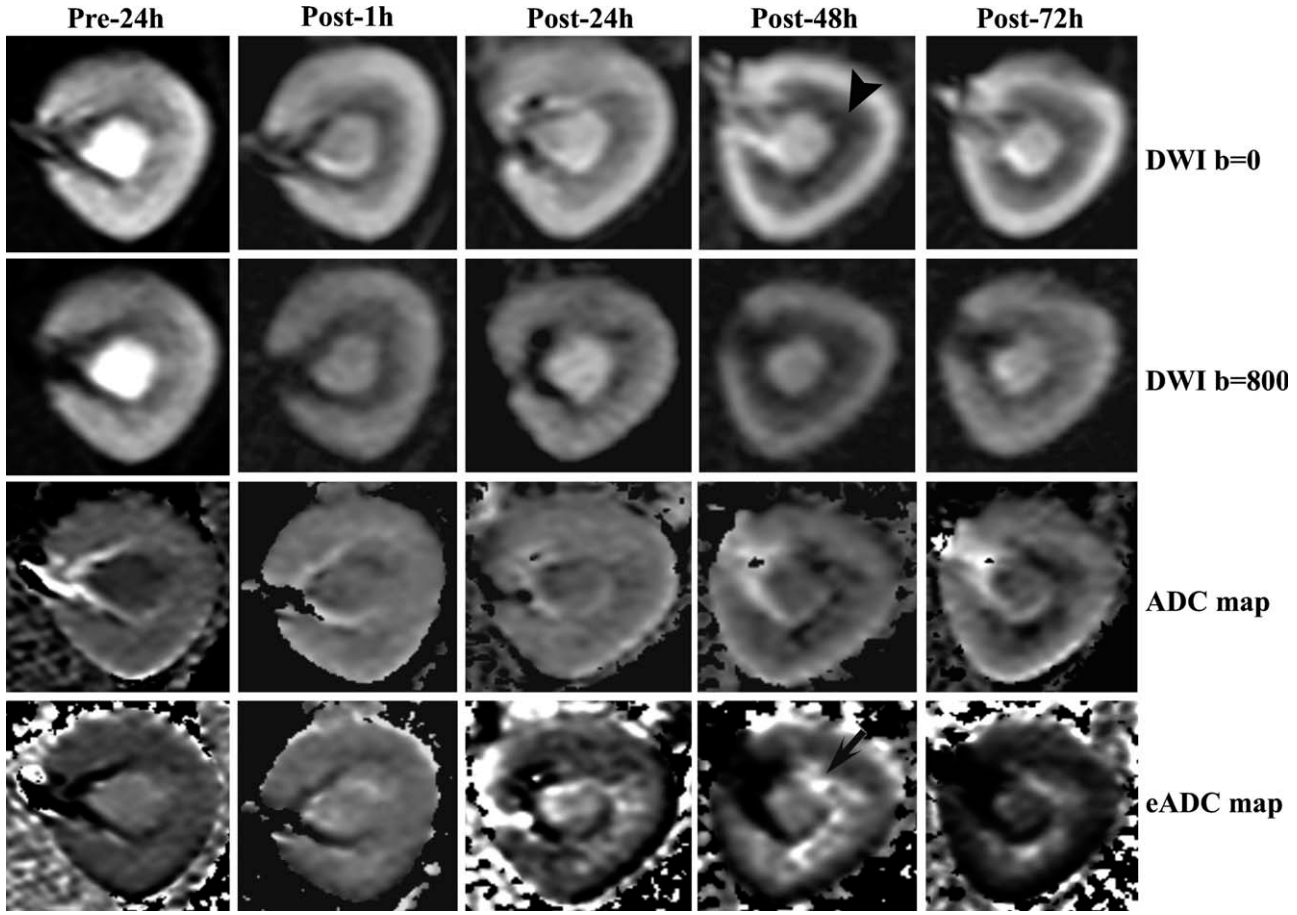

Figure 3. DW-MRI images obtained in a rabbit kidney before and after iopamidol injection. It shows that medullary signals on SE-EPI images (b = 0 s/mm^2) in the first row, DW images (b = 800 s/mm^2) in the second row and ADC images in the last row, are reduced as early as first h and aggravated heavily within 48 h (black arrowhead), but mildly alleviated in 72 h after injection. The remarkable hyper-intensity on medullary exponential ADC images (black arrow) indicates an impaired water transport function in this compartment due to iopamidol injection. The relative hyper-intensity on cortical DW images is possibly caused by T2-shielding effect, which is removed on ADC or exponential ADC images.

analysis on ADCs illustrated that the contrast-induced functional deficiency in renal parenchyma developed as early as 1 h after injection, aggravated and lasted within the subsequent 48 h, while slightly alleviated at 72 h after injection. This functional alternation in contrast-related kidney has not been reported in previous literatures. Based on the time course study, we supposed that the reduction of ADC values in early stage of contrast-induced kidney (proximately within the first h), may be partially caused by a transient vasoconstriction (26,27), while the reason for the delayed aggravation in diffusion deficiency within the subsequent 48 to 72 h, especially in the kidney of IS, is still unclear. The successive aggravation of diffusion deficiency may be caused by direct cytotoxic effect or delayed apoptosis in the tubule cells of the kidney distal segment. The direct cytotoxic effects of iodinated CM on the tubule cells were comprehensively investigated in the last decade. By exploring the porcine proximal tubule cell line and LLC-PK1 cells to iopamidol in an ex vivo environment, Hardiek et al (28) found that iopamidol did not affect cell viability, but reduced cell proliferation and produced a reversible inhibition of mitochondrial function. Moreover, their study also indicated that the disturbance of mitochondrial enzyme activity and mitochondrial membrane potential remained relatively unchanged up to 60 h after iopamidol treatment. As reported in another ex vivo experiment, a highly hyperosmolal, ionic radiocontrast agent diatrizoate can induce DNA fragmentation (apoptosis) in MDCK cells (29). Although we could not determine whether inhibition of mitochondrial function or delayed apoptosis in tubule cells is related to the functional changes in our DW-MR images, it is well known that the deficiency of mitochondrial enzyme activity can reduce the activity of adenosine triphosphate enzyme (ATPase), which may limit the ability of water transport function between extra- and intra-cellular. Our study demonstrated that the progressive ADC declines in the IS due to iopamidol injection were significantly greater than those estimated in CO, OS, or IM of kidney. The greatest change in ADCs was primarily found in the kidney of IS, where the tubule cells are vulnerable to cytotoxic effects of iodinated CM, which indicated that there may be some potential correlations between the signal changes in DW-MR images and the delayed cell apoptosis. Moreover, more pronounced

diffusion deficiency in the kidney of IS may be also associated with its lower tissue pO_2 (approximately 10–20 mmHg in the deeper portion of the outer medulla), which makes it more vulnerable to the contrast-induced nephrotoxicity.

The diffusion deficiency observed in our study may be also caused by the reduction in intrarenal water contents. Although the iopamidol-370 is categorized into a low-osmolality agent, its osmolality (796 mOsm/kg H_2O) is still much higher than that of blood plasma (313 mOsm/kg H_2O) (30,31). Thus with urinary concentration in distal segments of the kidney, as well as with the characteristics of hyperosmolality, the iopamidol accumulated in collecting ducts will lead to a progressive cellular dehydration, which results in relative decrease in intrarenal water contents.

One limitation of our experiments was that the number of animals included in the study was relatively small. One rabbit died at 24 h after the intravascular administration of iodinated contrast agent, due to an over-dose anesthesia. Although this may lead to a large standard deviation in the estimation of intrarenal ADC, significant results were still obtained. This indicates an advantage of noninvasive DW-MRI technique, which allows serial measurements to be performed in the same animal before and after the contrast injection, thus, each animal can act as its own control. Another limitation was that we did not obtain a histopathological data at the different time points to better relate these DW-MR trends to the pathogenesis of contrast-induced nephropathy. Furthermore, a multiple b-values technique should be used to investigate both contributions from blood perfusion and water diffusion in the further work.

In conclusion, our time course study indicated that DW-MRI is an alternative noninvasive method for quantitative evaluation of renal function in normal or contrast-associated rabbit kidney models. The 5-day sequential observation in our study demonstrated a persistent 72-h reduction in renal water transport function due to iodinated CM administration. Moreover, the medullary diffusion deficiency may be helpful to understand the pathogenesis associated with CIN.

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