Evaluation of the temporal variation of diffusion and micro-perfusion in cisplatin induced rodent renal fibrosis models using multi-b diffusion weighted MR imaging

Haoran Sun[1], Huanhuan Wu[1], and Ziheng Zhang[2]

[1]*Radiology, Tianjin Medical University Hospital, Tianjin, Tianjin, China,* [2]*MR Research China, GE Healthcare, Shanghai, Shanghai, China*

Introduction: Cisplatin (CP) is a highly active antineoplastic agent used in the treatment of cancers, but associated with nephrotoxicity, and prone to result in renal fibrosis with a long-term administration[1]. Diffusion weighted (DW) MRI techniques, based on the Brownian motions of water molecules between tissues and cells provide a non-invasive assessment of molecular diffusion and microcirculation in vivo. Intravoxel incoherent motion (IVIM)[2] DWI has recently shown a potential to assess kidney function, through the parameters that reflect changes in overall diffusion (apparent diffusion coefficient, ADC), perfusion fraction f, pseudo diffusion D* and true diffusion D[3]. The aim of this study is to evaluate the feasibility of the mono- and bi-exponential models through multi-b DW-MRI measurements in reflection of the temporal variation of diffusion and microperfusion on cisplatin induced rodent renal fibrosis models. Histopathological examinations were performed for reference.

Materials and Methods: This study was approved by Animal Care and Use Committee, Tianjin Medical University. Renal fibrosis was induced in 14 rats by intraperitoneal injection of cisplatin (4.5mg/kg) twice in two consecutive days. MR scanning were performed before and 2d, 4d, 6d, 8d, 2w, 3w and 4w after the injection at a 3.0T scanner (MR750, GE, USA) using an animal coil (Magtron, China). Besides T_1WI and T_2WI, a multi-b DW MR scan with 12 b values from 20 to 1500s/mm^2 was acquired. The results were analyzed using both mono- and bi-exponential model at Advantage Workstation (GE, USA) with the mappings of ADC, f, D* and D obtained, as illustrated in Fig. 1. The regions of interest (ROIs) on cortex (CO), outer stripe of the outer medulla (OM) and inner stripe of the outer medulla (IM) at the hilum level were selected. One model rat was scarified at each time point post MR acquisition for histopathological examination.

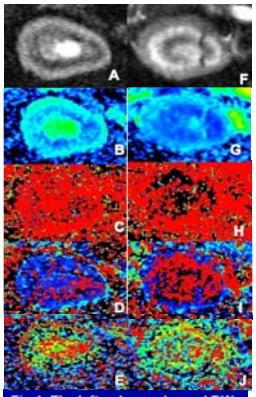

Fig 1. The left column showed DW images(b=0), ADC map, f map, D* map and D map of the right kidney of a normal rat(A-E). The right column showed the corresponding changes in the same kidney 2 days after cisplatin injection (F-J).

Results and Discussion: As shown on DW images, Fig. 1, COs shrinked while OMs broadened 2 days after CP injection with no significant change on IM stripes observed, suggesting the renal fibrosis phenomenon was mild. True but without shown, the severity of renal fibrosis deteriorated with time. From Fig. 2a, one can disclose ADCs of all three stripes decreased within the first four days and increased till the second week, then tended to be steady thereafter. The ADC of IMs decreased more significantly and failed back to normal. These changes reflected acute cytotoxic edema in the damaged parenchyma and self-repair occurred since 6 days when renal fibrosis predominant in the IMs[4]. The f values of all three stripes, as shown in Fig. 2b, decreased in a pattern of fluctuation, with the turning point at the 4th day for both IMs and OMs. The f values referred to the proportion of pseudo-diffusion in the overall diffusion effect. Thus the decrease of f value indicated a reduced renal micro perfusion. While the slight elevation of f afterwards implied the happening of vasogenic edema, commonly associated with cytotoxic edema. As illustrated in Fig. 2c, D* slowly increase in all three stripes, but IMs experienced an instant dropping-down at 4 days after injection. D* depends on the flow rate and spatial structure of the capillaries. Renal fibrosis resulted in a lessen vasculature and an increased blood flow velocity, which were intermingled together[5]. A continuously increased D* implied that in IM and OMs there existed less vasculatures than COs, but blood flow increased for compensating and repairing[6]. D values of all three stripes experienced a two-peak variation with the first peak happened four days after injection and the second happened two weeks after injection, Fig. 2d. Meanwhile the D value of IMs changed much more significantly than the other two with 1.8-fold elevation occurred at the second peak. Interestingly, the variation of D of all three stripes had almost opposite tendencies with ADC, the reason was unclear and under investigation. From histopathological examination, it was found renal tubular epithelial edema and inflammatory cell infiltration occurred 4 days after injection, Fig 3a, and renal fibrosis began to be predominant at 3 weeks, Fig 3b.

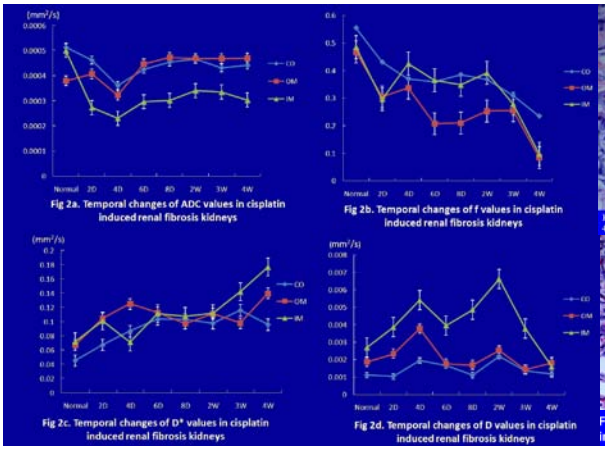

Fig 2a. Temporal changes of ADC values in cisplatin induced renal fibrosis kidneys

Fig 2b. Temporal changes of f values in cisplatin induced renal fibrosis kidneys

Fig 2c. Temporal changes of D* values in cisplatin induced renal fibrosis kidneys

Fig 2d. Temporal changes of D values in cisplatin induced renal fibrosis kidneys

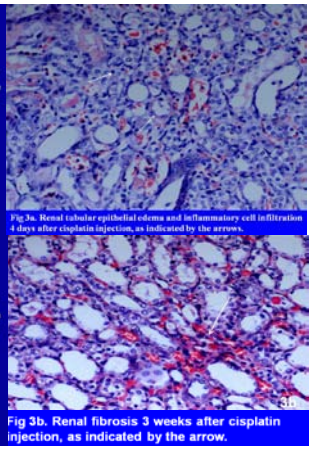
Fig 3a. Renal tubular epithelial edema and inflammatory cell infiltration 4 days after cisplatin injection, as indicated by the arrows.

Fig 3b. Renal fibrosis 3 weeks after cisplatin injection, as indicated by the arrow.

Conclusion: From the findings of this study, the ADC values behaved as a weight of the true diffusion D, and the pseudo-diffusion D*. The biomarkers resulted from mono-exponential model exhibited a dual phase temporal variation, while those from bi-exponential model remained a single tendency of variation. According to the histopathological observation, with the worsening of renal fibrosis, the bi-exponential model might be a better choice for an accurate indication of the evolution of renal fibrosis.

References: 1. Brady HR, et al., Am J Physiol 1990;258:F1181–7. 2. Le Bihan D, et al., Radiology1986; 161(2): 401-407; 3.Chandarana, H. et al. Invest Radiol, 2011. 46(5): 285-29; 4. Sigmund, E.E., et al., Radiology, 2012. 263(3): 758-69. 5. Dos Santos EA, et al., Invest Radiol 2007;42:157–62. 6. Sayed AA. Phytother Res 2009;23:1738–41.