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Original contribution

# A feasibility study of using noninvasive renal oxygenation imaging for the early assessment of ischemic acute kidney injury in an embolization model

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ABSTRACT

*Purpose:* To investigate the feasibility of using MRI based oxygenation imaging for early assessment of ischemic acute kidney injury (AKI) in an embolization model.

*Methods:* Ischemic AKI model was induced in 40 rabbits by injection of microspheres into the right renal arteries. Animals were grouped according to the dose of microspheres: Severe AKI group, 2.0 mg ($N = 10$); Moderate AKI group, 1.0 mg ($N = 10$); Mild AKI group, 0.5 mg ($N = 10$); Control group, saline without microspheres ($N = 10$). A serial MRI examination was performed at intervals of 1 h, 1 day, 1 week and 4 weeks to evaluate the deterioration of renal function. A multi-echo ASE sequence was implemented for renal oxygenation measurement 1 h after surgery. Pathological examinations were performed 4 weeks after the surgery.

*Results:* In renal cortex, renal oxygen extraction fraction (OEF) raised significantly after embolization procedures in all experimental groups (severe AKI: 0.39 ± 0.05, $P < 0.05$; moderate AKI: 0.36 ± 0.03, $P < 0.05$; mild AKI: 0.34 ± 0.02, $P < 0.05$) compared to the control group (0.29 ± 0.02). In outer medulla, significant difference was observed between control group (0.29 ± 0.03) and severe AKI group (0.35 ± 0.03, $P < 0.05$), and between control group and moderate AKI group (0.34 ± 0.04, $P < 0.05$). Corresponding lesions were found in pathological examinations 4 weeks after the procedure.

*Conclusion:* This study demonstrates the feasibility of using oxygenation imaging to assess the embolization induced ischemic AKI at an early stage.

## 1. Introduction

Acute kidney injury (AKI) is a potentially reversible syndrome that leads to renal inflammation, loss of renal function, and progressive fibrosis [1–3]. AKI occurs in various clinical settings with the incidence in the range of 3.2%–34% in hospitalization patients, and 67.2% in critically ill patients [4]. Cholesterol embolization syndrome (CES), which refers to embolization of the contents of an atherosclerotic plaque (primarily cholesterol crystals) from a proximal large-caliber artery to distal small to medium arteries causing end-organ damage by mechanical plugging and an inflammatory response, has been recognized as an important cause of AKI [5]. Due to the increase in the number of cardiovascular interventions, a growing number of iatrogenic renal dysfunction is caused by CES [5].

Conventional assessment of AKI is based on the changes in serum creatinine concentration and the amount of urine output [2]. However, these examinations can only reflect the overall renal function when substantial renal injury occurs, which are not sensitive for the early diagnosis. Some novel biomarkers have been used for early detection of AKI recently, but these indicators are not widely accepted [6].

Ischemic renal injury results from a complex pathophysiological process, in which tissue oxygenation changes during the deterioration

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of renal function [7]. Measurement of the renal oxygenation level could be helpful for the assessment of ischemic AKI before the current diagnosis criteria are met. Recently, an MRI-susceptibility based method has been proposed to quantify renal oxygenation levels noninvasively [8]. The proposed method used a cylinder susceptibility model for the quantification of renal oxygen extraction fraction (OEF) with the implementation of a asymmetric spin-echo (ASE) pulse sequence [8]. The MRI-based renal oxygenation measurement was reported to have good correlation relationship with the measurement of blood $pO_2$ [8], which seems to be promising for the early assessment of ischemic AKI noninvasively.

This study aims to investigate the feasibility of using the MRI based oxygenation imaging for the assessment of ischemic AKI at an early stage in an embolization model.

## 2. Materials and methods

### 2.1. Animal study

The experimental protocol was approved by our animal protection committee. All the experiments were conducted in accordance with the guidelines for animal care and experimentation.

A total of 40 New Zealand White rabbits (males, weight range: 2.5–3.5 kg) were included in this study. Digital subtraction angiography (DSA) examinations were performed using an angiographic unit (Innova 4100, GE Healthcare, Waukesha, USA) during the embolization procedure. During the procedure, animals were positioned supine on the angiographic table with a close-fitting facemask covering the whole mouth and nose. A flexible tube was connected to the mask, leading to air supply with a flow rate of 2.5 L/min. The animals were ventilated with isoflurane (2–3%) delivered by a calibrated vaporizer. Microspheres (Hepasphere, Merit, Rockland, USA) with diameters of 100–150 μm were injected into the right kidney of each animal by using a 4F catheter positioned at the ostium of renal artery. The embolization processes were conducted under the guidance of fluoroscopy at a low speed. Angiographies (flow velocity = 1.5 mL/s, flow time = 3 s) were performed before and after the embolization in all rabbits. The procedures were performed by an interventional radiologist with 6 years of experience. Diagram of the experimental protocol is shown in Fig. 1.

Animals were randomly grouped according to the dose of injected microspheres: Severe AKI group received 2.0 mg (approximately $5 \times 10^4$) of microspheres ($N = 10$); Moderate AKI group received 1.0 mg of microspheres ($N = 10$); Mild AKI group received 0.5 mg of microspheres ($N = 10$); and Control group received saline without microspheres ($N = 10$). The number of microspheres was counted in suspension with a microscopic magnification of 400.

Blood samples were collected from all animals 1 day before and at the end of 1 day, 1 week, 2 weeks and 4 weeks after the procedure. Serum creatinine levels were measured from the blood samples by using an automatic biochemistry analyzer (Reflotron system, Roche Diagnostics, Basel, Switzerland).

### 2.2. MR imaging

Renal MRI was carried out on a 3.0 Tesla clinical MRI scanner (Achieva, Philips Medical Systems, Best, Netherlands) using an 8-channel knee coil. Serial MR examinations were performed 1 h, 1 day, 1 week and 4 weeks after the surgical procedure to evaluate the dynamic changes of renal function.

A multi-echo ASE sequence, which is sensitive to tissue oxygenation, was implemented 1 h after the surgery for the purpose of early renal oxygenation measurement. The imaging parameters were: FOV = 120 × 120 $mm^2$, matrix size = 80 × 75, TR = 2000 ms, $TE_1/TE_2/TE_3$ = 60/88/116 ms, slice number = 8, slice thickness = 5 mm, SENSE factor = 2. A total of 32 images with shifted 180° pulses (shifted time from −16 to 15 ms with an increment of 1 ms) was acquired for each slice. Respiratory triggering was applied before image acquisition to reduce the respiratory motion artifacts. T2-weighted (T2w) images (TR/TE = 3500/70 ms) and diffusion-weighed (DW) images (TR/TE = 3000/65 ms, $b$ values = 0 and 1000 s/$mm^2$) were acquired subsequently. The T2w and DW images were acquired with identical geometric parameters as the ASE sequence for better comparisons between different imaging modalities.

### 2.3. Quantitative analysis

Images were transferred to a workstation for post-processing using a home-build software developed in the Matlab (MathWorks, Natick, MA). Rigid kidney registration was conducted using mutual information to reduce motion artifacts from respiratory movements. Prior to the calculation of renal oxygenation level, all the ASE images were filtered with a Gaussian low-pass filter (kernel size = 3 × 3, standard deviation = 1.5) to improve the signal-noise-ratio (SNR).

The calculation of tissue *OEF* was derived from a signal model based on the magnetic susceptibility effect of deoxyhemoglobins [9–12]. The detailed data analysis has been described in [8]. Briefly speaking, the MRI signal is written as follows:

$$S(\tau) = \rho(1-\lambda)\cdot f(\lambda, \delta\omega, \tau)\cdot \exp(-TE/T2)\cdot g(\tau, T1, TR) \quad (1)$$

in which ρ is the spin density; λ is the volume fraction of tissue occupied by the susceptibility sources; $f(\lambda,\delta\omega,\tau)$ is the susceptibility dependent function, which is simplified by an approximation at two different time scales; $g(\tau,T1,TR)$ is the T1 dependence term. If $TR \gg TE/2\text{-}\tau$, $g(\tau,T1,TR)$ can be approximated as:

$$g(\tau, T1, TR) \approx 1 - \exp(-TR/T1) \quad (2)$$

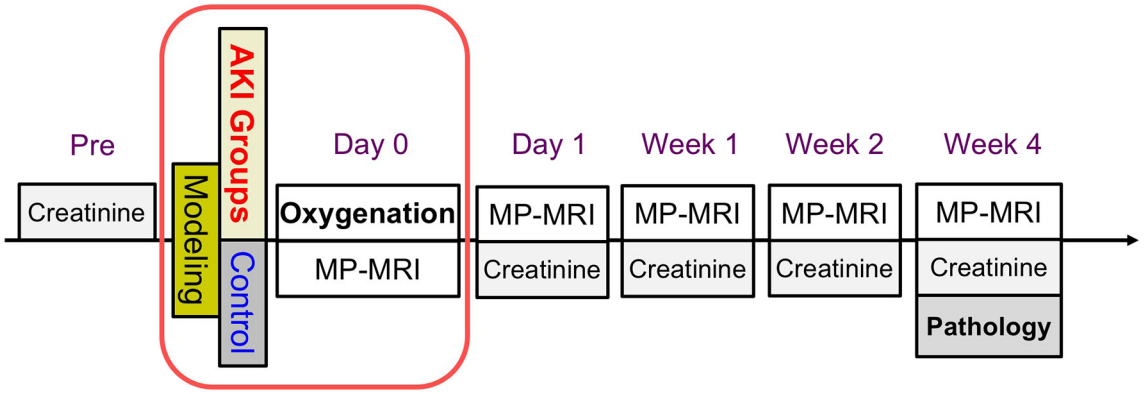


**Fig. 1.** Diagram of the experiment. Serial multi-parametric (MP) MRI, biochemical and pathological examinations were performed on Day 0, Day 1, Week 1 and Week 4 following the AKI modeling.

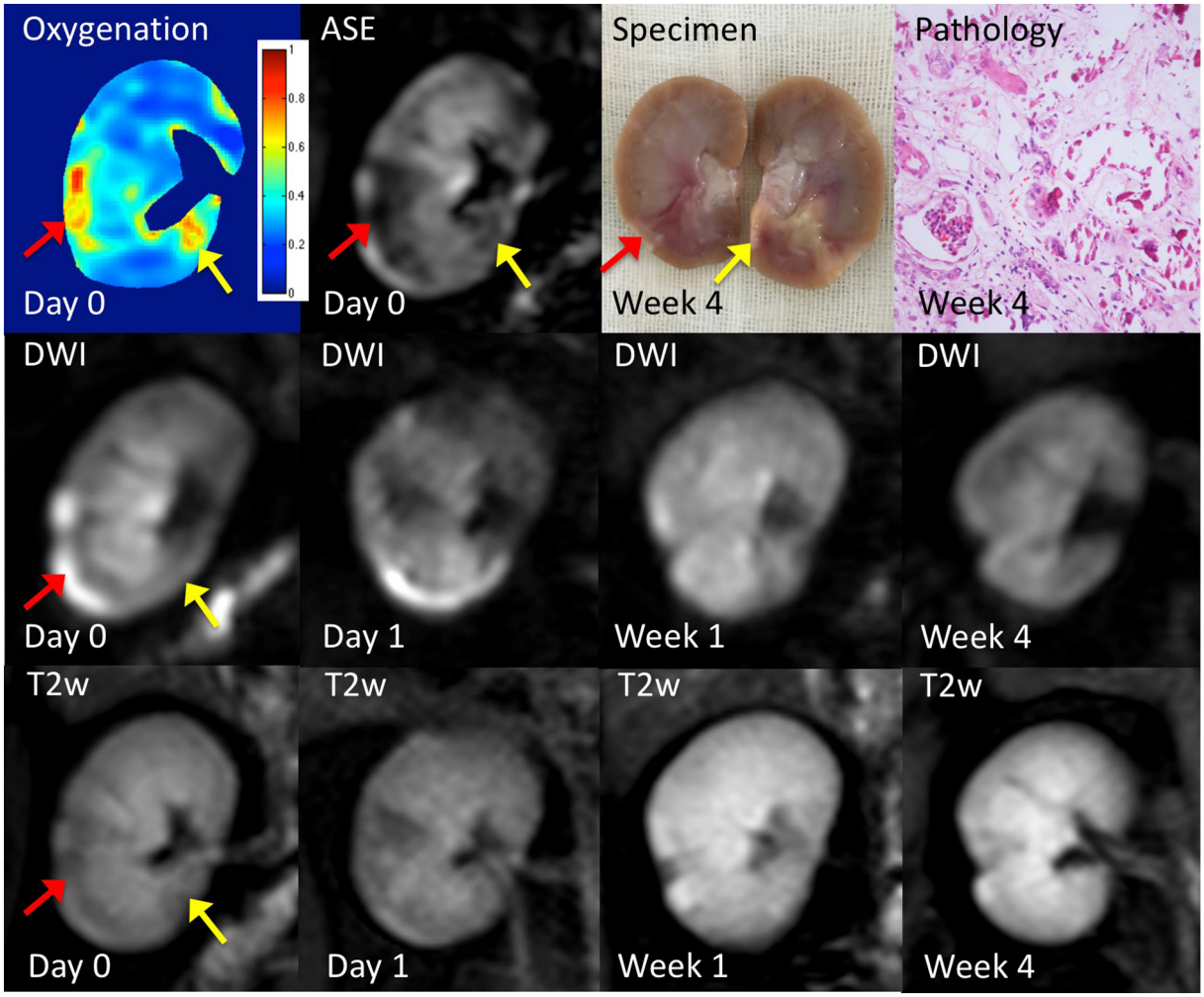


**Fig. 2.** Representative example of renal oxygenation map and raw ASE image (τ = 0 ms) obtained immediately after severe AKI modeling (Day 0, red and yellow arrows); T2w images and DW images (DWI) acquired immediately after procedure (Day 0), and obtained 1 day, 1 week and 4 weeks thereafter; pathological results obtained 4 weeks after procedure. The glomeruli show ischemic and wrinkled features with thickening of Bowman's capsule; necrosis of the renal tubular epithelial cells is observed, and the basement membrane is exposed; the brush borders of some tubular epithelial cells fall off; the tubular epithelial cells become flat and tubular lumen expands; renal interstitial fibrosis can be seen. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

According to the model proposed by Yablonskiy et al. [9], the MR signal can be approximated at two time scales as:

$$S_L(\tau) = \rho(1-\lambda)\cdot\exp(-\lambda\cdot\delta\omega\cdot 2\tau + \lambda)\cdot\exp(-TE/T2)\cdot(1-\exp(-TR/T1)) \quad (3)$$

for $\delta\omega\ 2|\tau| > 1.5$, and

$$S_S(\tau) = \rho(1-\lambda)\cdot\exp(-0.3\lambda\cdot(\delta\omega\cdot 2\tau)^2)\cdot\exp(-TE/T2)\cdot(1-\exp(-TR/T1)) \quad (4)$$

for $\delta\omega\ 2|\tau| < 1.5$, where $\delta\omega$ is the characteristic frequency shift that is defined as:

$$\delta\omega = \frac{4}{3}\pi\cdot\gamma\cdot\Delta\chi_0\cdot Hct\cdot B_0\cdot OEF \quad (5)$$

where γ is the gyromagnetic ratio; $\Delta\chi_0$ is the susceptibility difference between fully oxygenated and fully deoxygenated blood; *Hct* is the fractional hematocrit. In this study, *Hct* of 0.4 was employed for all subjects. The reversible relaxation rate *R2'* was defined as:

$$R2' = \lambda\cdot\delta\omega \quad (6)$$

### 2.4. Histopathology exam

Four weeks after the embolization procedure, animals were executed and the experimental kidneys were perfused via left ventricle with saline solution (~0.9%) until the renal cortex were completely cleared of blood. Tissue samples were removed immediately after perfusion and embedded in paraffin. The paraffin sections were then stained with hematoxylin and eosin (H&E) for histological examinations. The histological analysis was performed by a pathologist with > 12 years of experience.

### 2.5. Statistical analysis

All statistical analysis was performed by using Origin software (version 10.2). For each compartment, i.e., cortex (CO), outer medulla (OM), and inner medulla (IM), representative ROIs were manually drawn on the T2w images by an experienced abdominal radiologist (with 5 years of imaging experience). The ROIs were placed to avoid fatty tissues of renal sinus and blood vessels. Data were reported as mean ± standard error. Renal OEFs measured at different time points following AKI were compared using one-way analysis of variance (ANOVA). Relative OEF (rOEF) was defined as the oxygenation level

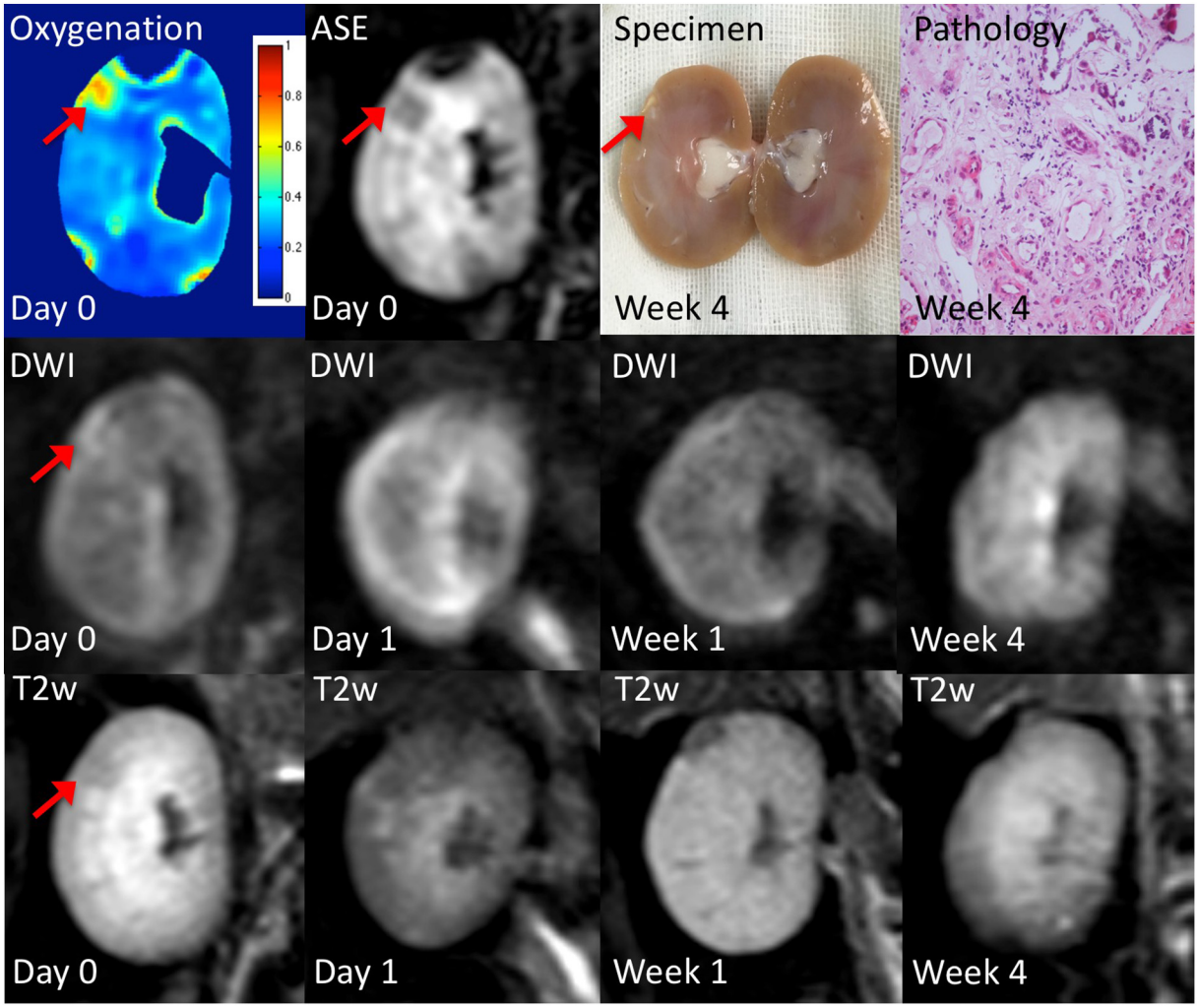


**Fig. 3.** Representative example of renal oxygenation map and raw ASE image ($\tau$ = 0 ms) obtained immediately after moderate AKI modeling (Day 0, red arrows); T2w images and DW images (DWI) acquired immediately after procedure (Day 0), and obtained 1 day, 1 week and 4 weeks thereafter; pathological results obtained 4 weeks after procedure. The glomeruli show ischemic and wrinkled features with dilated change of Bowman's capsule; abscission and partly necrosis of the renal tubular epithelial cells, tubular ectasia and cellular debris are observed, protein cast can be seen occasionally; focal inflammatory cells infiltrate in renal interstitium. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

measured from the AKI kidney divided by the measurement from contralateral healthy kidney. Correlations of rOEFs and serum creatinine were assessed by using Pearson coefficient of correlation. $P$ values < 0.05 were considered to indicate a significant difference.

## 3. Results

Eight rabbits died during the embolization procedure (two in each group). Renal MRI imaging was successfully conducted in all the remaining rabbits ($N$ = 32). Three representative examples of ischemic AKI are shown in Figs. 24 (corresponding to severe, moderate and mild AKI, respectively). The rabbit with severe AKI (Fig. 2, red arrows) shows a large region of increased renal OEF after renal embolization. The lesion can also be noticed in DW and T2w images. The resected specimen clearly revealed the renal lesion in the severe AKI rabbit. The rabbit with moderate AKI (Fig. 3) demonstrated a region of elevated OEF that is less obvious in both DW and T2w images (red arrows). In both rabbits, the lesions defined by the increase of OEF were confirmed by the pathological results. The rabbit with mild embolization (Fig. 4) demonstrated less increase of renal OEF after the surgery. No abnormal signals were found in the follow-up T2w scans, but renal ischemia status can be noticed in the pathological examination 4 weeks after the surgery (yellow arrows).

Renal OEFs raised significantly in all the experimental groups (severe AKI: 0.39 ± 0.05, $P$ < 0.05; moderate AKI: 0.36 ± 0.03, $P$ < 0.05; mild AKI: 0.34 ± 0.02, $P$ < 0.05) in renal cortex compared to the control group (0.29 ± 0.02) (Fig. 5). While in the outer medulla, significant differences of OEFs were observed between the control group (0.29 ± 0.03) and the severe AKI group (0.35 ± 0.03, $P$ < 0.05), and between the control group and the moderate AKI group (0.34 ± 0.04, $P$ < 0.05). No significant difference was found between the control group and the mild AKI group (0.31 ± 0.03, $P$ = 0.50). In the inner medulla, no significant difference was observed between the control group and any AKI group (severe AKI vs control: 0.35 ± 0.03 vs 0.33 ± 0.03, $P$ = 0.21; moderate AKI vs control: 0.32 ± 0.03 vs 0.33 ± 0.03, $P$ = 0.58; mild AKI vs control: 0.33 ± 0.03 vs 0.33 ± 0.03, $P$ = 0.81).

Instead of calculating OEF in the whole cortex or medulla, the regional increased OEFs were also measured and found to be higher than the control group (0.48 ± 0.03 in severe group; 0.45 ± 0.04 in moderate group; 0.41 ± 0.05 in mild group, all $P$ < 0.05). Significant difference was seen between severe and mild AKI groups ($P$ < 0.05), and moderate and mild AKI groups ($P$ < 0.05). Besides, the changes of kidney sizes (defined as the ratio of length measured 4 weeks after the

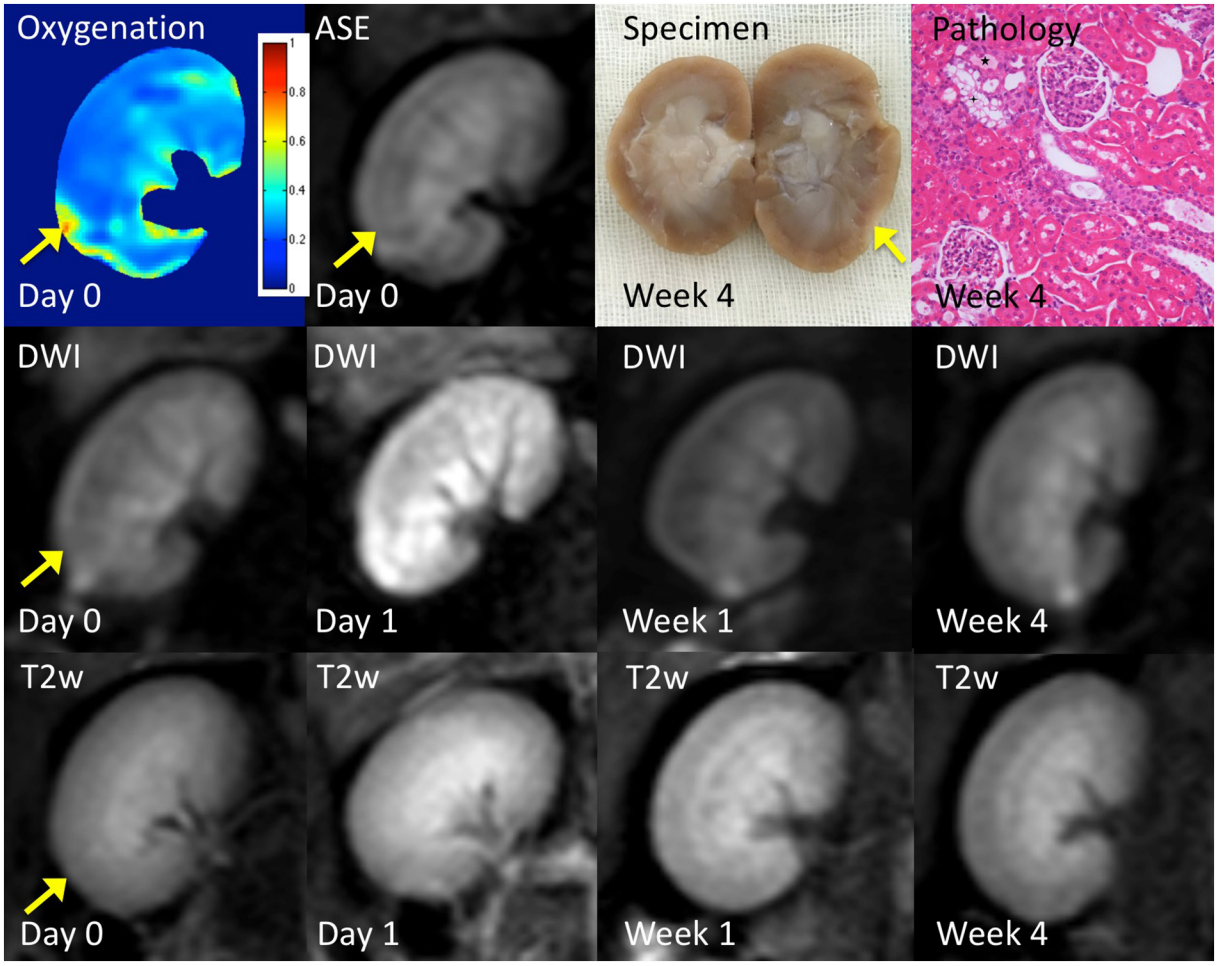


**Fig. 4.** Representative example of renal oxygenation map and raw ASE image (τ = 0 ms) obtained immediately after mild AKI modeling (Day 0, yellow arrows); T2w images and DW images (DWI) acquired immediately after procedure (Day 0), and obtained 1 day, 1 week and 4 weeks thereafter; pathological results obtained 4 weeks after procedure. The glomeruli appear basically normal; renal tubules appear basically normal while mild vacuole degeneration occurs in a few renal tubular epithelial cells and part of the renal tubulars have protein cast; renal interstitium is normal. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

procedure to pre-procedure length) were not significant in all experimental groups (severe AKI: 0.94 ± 0.11; moderate AKI: 0.92 ± 0.10; mild AKI: 1.10 ± 0.15; control group: 1.01 ± 0.03).

The serum creatinine levels at day 1 increased significantly in the severe AKI (from 85.25 ± 18.35 μmol/L to 153.88 ± 74.56 μmol/L, $P < 0.05$) and moderate AKI groups (from 96.50 ± 15.68 μmol/L to 142.88 ± 34.19 μmol/L, $P < 0.05$), marginally significantly in the mild AKI group (from 99.00 ± 6.59 μmol/L to 124.13 ± 34.13 μmol/L, $P = 0.06$) and not significantly in control group (from 89.01 ± 10.86 μmol/L to 87.63 ± 9.62 μmol/L, $P = 0.48$) as shown in Fig. 6. Serum creatinine levels declined in all groups one day after surgery.

## 4. Discussion

This study demonstrates the feasibility of using MRI based oxygenation imaging for the early assessment of ischemic AKI in an embolization animal model. Significant elevation of renal oxygenation levels was seen in renal cortex (all groups) and outer medulla (severe and moderate AKI groups). Renal injuries were observed 4 weeks after the surgical procedure in the pathological findings. The increased OEF defined lesions had higher oxygenation levels in the AKI groups compared to that in control groups. The findings were in line with the severity of ischemic AKI. The MRI based renal oxygenation measurement seems to be an effective in the assessment of AKI and is capable of staging different severity of renal injuries according to our findings.

Patients with ischemic AKI are asymptomatic at an early stage until there has been enough parenchymal damage to cause an elevation in creatinine or reduction in urine output. Although AKI is potentially reversible, there are chronic consequences even if the patients survive their acute illness, with a high risk of developing or exacerbating chronic kidney disease (CKD) and hastened development of end-stage renal disease (ESRD) or death [6]. Early diagnosis and initiation of treatment can be helpful in the recovery of renal function [4]. Therefore, early assessment of AKI is of key importance to improve the clinical outcomes.

As reported previously, persistent abnormal perfusion after renal injury appears to be an important factor in the pathogenesis of AKI, and may contribute to the impairment of renal function [13,14]. Although have been introduced in diagnosing renal diseases for many years, perfusion imaging techniques are still immature. Local tissue hypoxia, on the other hand, is a direct consequence of abnormal perfusion, and could be used as an alternative biomarker to evaluate renal injuries. MRI based blood oxygen level-dependent (BOLD) technique, which uses oxyhemoglobin/deoxyhemoglobin as endogenous contrast agency to probe tissue oxygenation, has been explored for the characterization of renal parenchyma oxygenation in recent years [15-18]. However, BOLD imaging suffers from the complexity of signal sources, including local blood oxygen saturation, vascular geometry, hematocrit and blood flow and blood volume, which makes it difficult to be interpreted [19].

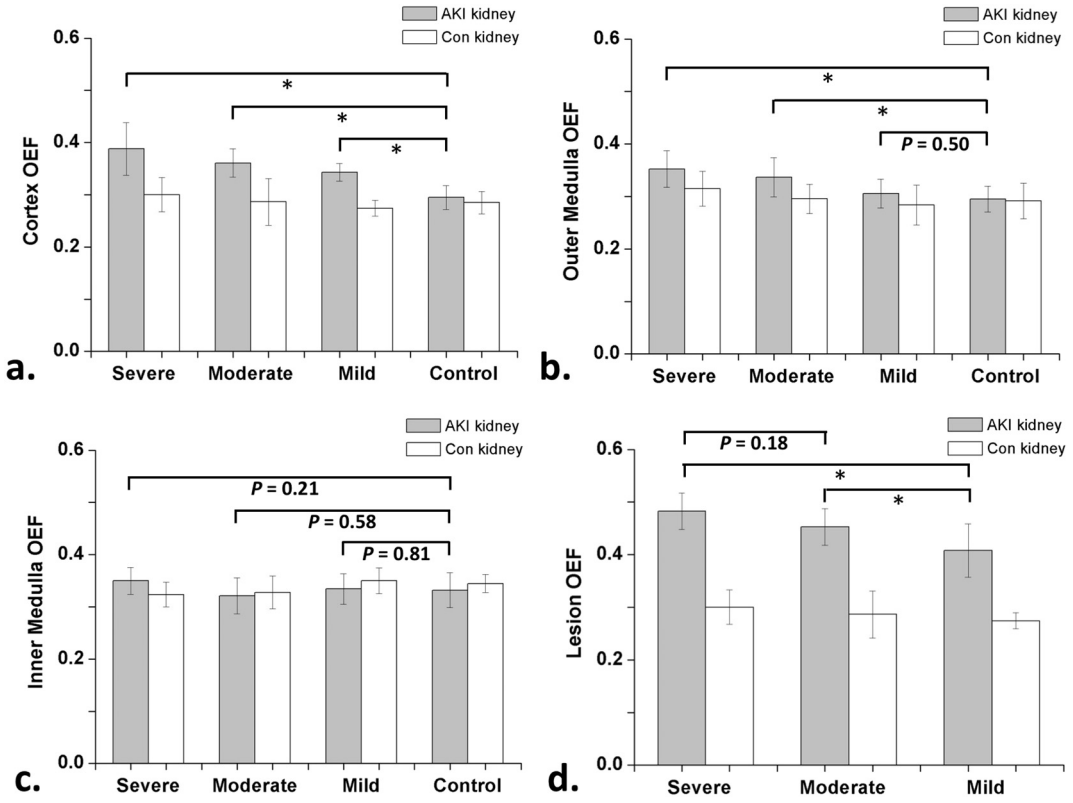


**Fig. 5.** The average renal OEFs in cortex (a), outer medulla (b), inner medulla (c), and focal lesion areas (d) measured immediately after embolization procedure in different groups.

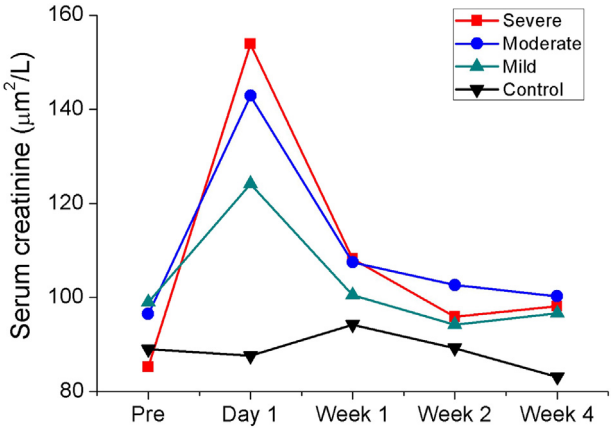


**Fig. 6.** The serum creatinine levels at baseline and after the embolization procedure in different groups.

Besides, it is often difficult to apply BOLD imaging in longitudinal studies and to compare signal changes across subjects due to its qualitative nature. Additionally, although BOLD imaging allows the measurement of T2* relaxation time, it cannot distinguish whether those alterations in $pO_2$ levels are caused by changes of the oxygen supply (e.g., arterial blood supply) or changes of oxygen consumptions.

Renal OEF is obtained by applying a susceptibility model to quantify the extraction fraction of oxygen by tissues, which is more reliable for the assessment of tissue ischemic status. Bias and reproducibility are greatly reduced in oxygenation imaging compared to BOLD scans. The MR based oxygenation imaging can not only be used for comparison studies among different individuals, but also can be applied to longitudinal studies in the same individual. The efficacy of the applied renal oxygenation measurement was validated previously through comparison with blood $pO_2$ [20]. Our study further proved that OEF measurement can provide quantitative parameters to evaluate renal oxygen extraction rate and assess different severity of renal injuries at an early stage.

In the post-ischemic kidney, cortical and inner medullary blood flow recovers following reperfusion, however, outer medullary blood flow remains compromised for prolonged periods of time [7]. In our study, the OEFs in inner medulla remained stable after surgery, while the OEFs in cortex and outer medulla evaluated after the surgery. This phenomenon can be explained to the sustained reduction in regional blood flow in the outer medulla.

There are several limitations in this study. First, single-shot echo planar imaging (EPI) is utilized for the readout of oxygenation imaging since it is less susceptible to respiratory motion. However, single-shot EPI readout has limitation in spatial resolution and is quite sensitive to the magnetic susceptibility at the interfaces of superficial tissues, blood, and fecal matter in the rectum. Multi-shot EPI acquisition or targeted FOV imaging are alternative approaches for higher spatial resolution imaging. Optimization of this technique should be considered in future studies. Second, we did not measure renal perfusion in this study. The consideration was that Gd-based contrast agency used in dynamic contrast enhanced (DCE) imaging might influence the oxygenation imaging signal. And the contrast agency will affect renal function within a long period of time. Non-contrast based perfusion technique, e.g., arterial spin labeling (ASL), might be an alternative approach for perfusion imaging. Third, a time course of renal OEF would be more insightful for the explanation of the progress of ischemic AKI. The reason that we only performed OEF measurement once due to considerations that 1) we are more interested in early detection and assessment of ischemic AKI (within 1 h after embolization), and 2) the experimental setting of OEF measurement is more complicated than T2w and DWI imaging, local high-order B0 shimming is required and respiratory triggering is needed before image acquisition to reduce the

respiratory motion artifacts. Besides, motion correction and registration are also necessary for OEF estimation. Those settings are time-consuming to be conducted at all time points. But it is obvious that a time course of OEF measurement will be more interesting and should be performed in our subsequent researches. Fourth, our animal model does not include the process of reperfusion and cannot be used to evaluate the ischemia-reperfusion injury (IRI) caused by kidney transplantation. Further studies should be performed on IRI models.

## 5. Conclusions

In conclusion, this study proved the feasibility of using MRI based oxygenation imaging for early assessment of ischemic AKI in an embolization animal model. Significant elevation of renal oxygenation levels was seen in both renal cortex and outer medulla. Experimental results showed the capability of oxygenation imaging in the staging of different severity of renal injuries at a very early stage.

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