The serial effect of iodinated contrast media on renal hemodynamics and oxygenation as evaluated by ASL and BOLD MRI

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Contrast-induced nephropathy is a prevalent cause of renal failure, and the mechanisms underlying this injury are not fully understood. We utilized noninvasive functional MRI in order to determine the serial effect of a single administration of iodinated contrast media (CM) on renal hemodynamics and oxygenation. Fifteen rabbits were randomized to receive an intravenous injection of CM (i.e. iopamidol-370; 6 ml kg\textsuperscript{-1} body weight) or an equivalent amount of 0.9\% saline. Both arterial spin-labeling and blood oxygen level-dependent imaging sequences were performed at 24 h before and at intervals of 1, 24, 48 and 72 h after injection to obtain serial renal blood flow (RBF) and relative spin–spin relaxation rate ($R_2^*$).

Results showed that, in the iopamidol group, the mean cortical RBF decreased at 1 h ($p = 0.04$ vs baseline), reached its minimum at 24 h ($p = 0.01$) and gradually returned to baseline by 48 h ($p = $nonsignificant, NS). The outer medullary RBF decreased to its minimum by 24 h ($p = 0.00$) and remained less than baseline until 72 h. $R_2^*$ in inner stripes was dramatically increased at 1 h ($p = 0.00$), remained elevated at 24 h ($p = 0.05$), but returned to baseline by 48 h ($p = NS$). $R_2^*$ values within the cortex and outer stripes and inner medulla were slightly increased, but the changes did not reach a statistical significance ($p = NS$). Saline did not produce positive change in either RBF or $R_2^*$ within different compartments of the kidney. We conclude that iopamidol is associated with a relatively longer-term hypoperfusion in whole kidney and decreased oxygen level in the inner stripes of the outer medulla. Copyright © 2012 John Wiley & Sons, Ltd.

Keywords: MRI; arterial spin-labeling; blood oxygen level-dependent; contrast-induced nephropathy; oxygenation; perfusion

1. INTRODUCTION

Contrast-induced nephropathy (CIN) is an iatrogenic event caused primarily by intravascular injection of iodinated contrast media (CM) (1–4). As the use of iodinated CM during radiological or interventional procedures increases, CIN has become one of the most prevalent causes of acute renal failure, especially in patients suffering from diabetes or cardiovascular pathology (5–7). The pathogenesis of CIN is not yet completely understood.

Altered intra-renal hemodynamic changes and increased vulnerability of the renal outer medulla to hypoxia are closely associated with CIN (8–10). CM produces prominent renal vasoconstriction and medullary hypoxia and exerts direct toxic effects on renal epithelial cells (11). However, as available data are primarily restricted to the first hour after administration, long-term effect of CM on renal hemodynamics and oxygenation are unknown. Previous research on CIN has also been limited by the methods used to determine renal blood flow (RBF) and partial pressure of oxygen (pO\textsubscript{2}). For example, the laser-Doppler probe and Clark-type microelectrodes (12) are unable to measure hemodynamics and oxygenation in the global kidney. Moreover, the invasiveness of these methods disallows the longitudinal studies.

In recent years, noninvasive MR techniques are reported to be able to obtain functional characteristics of the kidney. Arterial spin-labeling (ASL) MRI obtains reliable quantitative renal perfusion by tagging the endogenous water in capillaries as a tracer agent (13). Blood oxygen level-dependent (BOLD) imaging is capable of quantifying the tissue oxygenation under different pathophysiologic conditions (14–16). Accordingly, we aimed to quantify the functional response to iodinated CM injection, as compared with a placebo, in 15 healthy rabbits using ASL and BOLD MRI. We hypothesized that these techniques would be sensitive to changes in renal hemodynamics and oxygenation following iodinated CM injection, and more specifically, that the CM injection would result in a longer-term effect on perfusion and oxygenation throughout the kidney. As such, the work would be helpful to explain an important clinical issue that the serum creatinine (Scr) level in patients with CIN commonly arrives at the peak within 2–5 days after CM administration (17).

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2. EXPERIMENTAL

2.1. Theory of ASL

As the blood supply to the center-positioned slice of the kidneys does not consistently enter through a known side of the slice, the flow-sensitive alternating inversion–recovery (FAIR) tagging method has been applied to renal ASL to ensure the tagging efficiency of inflowing arterial blood. By using FAIR-ASL, arterial blood was tagged as an endogenous tracer over a relatively large area proximal to the imaging slice by a single inversion pulse. Sequential images, referred to as tag and control, were acquired in which blood was inverted (nonselective inversion) and not inverted alternately (selective inversion). To estimate arterial blood was tagged as an endogenous tracer over a relatively large area proximal to the imaging slice by a single inversion pulse. Sequential images, referred to as tag and control, were acquired in which blood was inverted (nonselective inversion) and not inverted alternately (selective inversion). To estimate the presence of arterial blood. By using FAIR-ASL, arterial blood was tagged as an endogenous tracer over a relatively large area proximal to the imaging slice by a single inversion pulse. Sequential images, referred to as tag and control, were acquired in which blood was inverted (nonselective inversion) and not inverted alternately (selective inversion). To estimate regional RBF, a time-dependent solution of the extended Bloch equation is given by Detre et al. (18):

\[
 f = \frac{\lambda}{2\pi} \times \frac{\Delta M(T1)}{M0} \times \exp \left( \frac{T1}{T1} \right)
 = \frac{\lambda}{2\pi} \times \left( \frac{M_{tag} - M_{control}}{M0} \right) \times \exp \left( \frac{T1}{T1} \right)
\]  

(1)

where \( f \) represents the tissue-specific blood flow (measured in milliliters per 100 g per minute), \( M_{tag} \) and \( M_{control} \) are the longitudinal magnetization of water per gram of tissue under tagging and controlling, \( M0 \) is the renal parenchyma equilibrium magnetization value, \( T1 \) is the longitudinal relaxation time of renal tissue, and \( \lambda \) is the blood tissue water partition coefficient, which is thought to be approximately constant at 90 ml per 100 g.

2.2. Animals and MR examination

This study was approved by the university animal care and use committee. Eighteen New Zealand white rabbits (male, body mass range 2.5–3.0 kg) were included. The rabbits were given free access to standard feed and tap water until the day of experiment. They were anesthetized with 5% pentobarbital sodium (dosage = 0.5 ml kg\(^{-1}\) body mass) via a venous cannula (24 G) inserted in marginal ear vein. During MR examination, the rabbit was placed in a supine position and the abdomen was firmly bound with a belly band to limit the motion of kidney.

Experiments were conducted on a 3.0 T whole-body MR scanner (Signa Excite\(^{TM}\); GE Medical Systems, Milwaukee, WI, USA) with a quadrature birdcage coil. The FAIR-ASL was combined with a single-shot fast spin-echo (SSFSE) sequence. A single axial plane through the center of left kidney was determined with the following imaging parameters: repetition time (TR), 3500 ms; echo time (TE), 60 ms; flip angle (FA), 90°; bandwidth, 62.5 kHz; slice thickness set to 5 mm, with an inversion slice thickness of 30 mm, to avoid artifacts from not fully inverted spins at the margins of the readout slice. A matrix of 128 \times 128 was used, with a field of view (FOV) of 12 cm\(^2\). For each slice, six image pairs were accumulated to obtain the two averaged FAIR images, with an inversion time (TI) of 1400 ms. \( M0 \) images were acquired using SSFSE without FAIR preparation, the imaging parameters of which were same as the FAIR–SSFSE sequence as described above, while the TR was converted to 6000 ms to ensure a complete relaxation of the spins between measurements. The total measurement time for one slice was within 1 min. TI images were recorded using an inversion–recovery SSFSE protocol with variable TIs (50–2000 ms). The parameters in this study were: TE, 48.2 ms; TR, 10 000 ms; matrix size, 224 \times 224; FOV, 12 cm\(^2\); bandwidth, 62.5 kHz; number of slices, 5; acquisition time at each TI, 45 s.

An axial, multiple-echo spoiled gradient recalled echo (SPGR) protocol through the center of left kidney was prescribed with 12 time echoes (TEs), as well as with the following parameters: TR, 100 ms; TE, 2–19 ms; FA, 45°; bandwidth, 31.25 kHz; matrix, 128 \times 128; FOV, 12 cm\(^2\); section thickness, 5 mm; section number, 6–8. The relative spin–spin relaxation rate (\( R_2^* = \frac{1}{T_2^*} \)), which is related to the concentration of deoxyhemoglobin in venous blood vessels, was employed as a BOLD parameter, such that a decrease in \( R_2^* \) implies an increase in tissue pO2.

As both the ASL and BOLD techniques are influenced by different factors (i.e. blood pressure, blood oxygenation levels, blood volume, hematocrit and water content), we acquired at the least three consecutive RBF and \( R_2^* \) maps within 1 h per day for three days in three healthy rabbits before the experiment. Their mean and standard deviations were reported to demonstrate the reliability of FAIR-ASL and BOLD MRI for this experimental protocol.

The 15 rabbits were randomized into iopamidol (\( n = 10 \)) and control (\( n = 5 \)) groups. The FAIR-ASL and BOLD images were acquired before CM injection to obtain baseline measures. After a 24 h control period, the rabbits received an intravenous injection of a nonionic, hyperosmotic iodinated CM, iopamidol-370 (Isovue, 370 mg I ml\(^{-1}\), 796 mOsm kg\(^{-1}\) H2O, Bracco Diagnostics Inc.) with a dosage of 6 ml kg\(^{-1}\) body weight or an equivalent amount of 0.9% saline. A serial MR examination was then performed at intervals of 1, 24, 48 and 72 h following injection to observe the dynamic response of intra-renal perfusion and oxygenation.

2.3. Post-processing

Prior to calculating RBF and \( R_2^* \), images were first filtered by using a Gaussian low-pass filter (the size of the kernel is 3 \times 3, and the standard deviation is 1.5) to improve the signal-noise-ratio (SNR). ASL data were post-processed using a home-made program written with MATLAB language (MathWorks Inc. Natick, MA, USA). The program allowed the registration of respiratory movements using a nonlinear method before the data evaluation. Magnitude images with section-selective and global inversion collected in two sets were averaged and the final images were subtracted. We constructed \( T1 \) relaxation maps from IR images with variable TI\(_s\) by fitting the signal intensity values to a mono-exponential curve. From the \( T1 \) maps in three rabbits used for reliability testing, the mean cortical and medullary \( T1 \) value was set at 1200 and 1600 ms, respectively, and averaged at 1400 ms for the global kidney. Then, the quantitative perfusion images were calculated on a pixel-by-pixel basis by using eqn (1). Pixels with a high perfusion of more than 600 ml 100 g\(^{-1}\) min\(^{-1}\) in the renal cortex or more than 250 ml 100 g\(^{-1}\) min\(^{-1}\) in the medulla were excluded from the evaluation. Region of interest (ROI) analysis was used to calculate region-specific RBF. The \( M0 \) image can provide the renal anatomical information to facilitate placement of the ROIs. Quantitative RBF covering the entire cortex and outer medulla was obtained by manually drawing its contour on the \( M0 \) image (Fig. 1). When evaluating the time series, the similar ROI locations were utilized for each image in the series. \( R_2^* \) maps were constructed with FUNCTool on a GE ADW 4.2 workstation, by fitting the signal intensity values to a mono-exponential curve. The SPGR image at the longest TE was provided to facilitate placement of the ROIs. Quantitative estimates of \( R_2^* \) were obtained within manually drawn ROIs (approximately 20–30 mm\(^2\)), including cortex (CO), outer stripes of the outer medulla (OS), inner stripes of the outer medulla (IS) and inner medulla (IM; Fig. 2). The region with artifacts caused by magnetic susceptibility effect was not included.
2.4. Statistical analyses

Descriptive statistics (mean ± standard deviation, SD) were used to summarize all variables. To determine the time-dependent differences and changes of RBF and $R_2^*$ in the different renal structures for pre- and post-administration of agents across the two groups, a one-way ANOVAs with Fisher’s least significant difference (LSD) test was used. $p$-Values of less than 0.05 were considered to indicate a statistically significant difference.

3. RESULTS

One rabbit died from over-dose of anesthesia at 24 h following intravascular administration of iopamidol; data from this rabbit were discarded. The other 17 rabbits successfully completed the entire protocol. MRI data of the left kidney were successfully recorded in all rabbits. As the belly band bound to the upper abdomen led to a marked shift of right kidney toward the thoracic cavity, only three rabbits underwent the overall ASL imaging and two rabbits underwent the baseline and post 1 h BOLD imaging in the right kidneys.

The ASL images used as RBF measurement revealed enough spatial information to visually determine tissue contrast between the cortex and outer medulla of the kidney. Images with motion artifacts were manually registered to facilitate the pixel-wise perfusion evaluation. Figure 1 illustrates three pairs of magnitude images with section-selective and global inversion, $M_0$ from a magnitude image and corresponding RBF map through the center of the left kidney. There is evidence of minimal motion artifact and that an excellent perfusion image is obtained.

Figure 1. Representative axial ASL images of one rabbit kidney. Three magnitude images with global inversion (a); magnitude images with section-selective inversion (b); $M_0$ from a magnitude image (c) that facilitates (1) identification of different structures of the kidney (cortex, outer and inner medulla) for drawing regions of interest (ROI); (2) acquisition of quantitative renal blood flow (RBF) map (d).

Figure 2. Resected specimen (a) and SPGR image at the longest TE for ROI drawing (b) clearly reveal four different layers of the kidney: cortex (CO; white arrow), outer stripes of the outer medulla (OS; black arrow), inner stripes of the outer medulla (IS; white arrowhead), and inner medulla (IM; black arrowhead). Experimentally measured TE-dependent signal intensities in four ROIs are fitted to a mono-exponential curve (c). Slope of the curve represents tissue $R_2^*$ (d).

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Figure 3. RBF and renal $R_2^*$ measured within 1 h per day for 3 days in three rabbits. Variations in mean RBF and $R_2^*$ were evident but did not statistically differ from one another over time.

Figure 4. Consecutive three-day arterial spin-labeling (ASL) and blood oxygen level-dependent (BOLD) images of one rabbit without saline or iopamidol injection. RBF and $R_2^*$ within each kidney structure were visually stable over time.

Table 1. Renal blood flow (RBF) changes following iopamidol-370 and saline administration (means ± SD)

<table>
<thead>
<tr>
<th>Time</th>
<th>Saline (n = 5)</th>
<th>Iopamidol (n = 9)</th>
<th>Saline (n = 5)</th>
<th>Iopamidol (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cortical RBF</td>
<td></td>
<td>medullary RBF</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>338.0 ± 93.5</td>
<td>320.5 ± 67.3</td>
<td>142.9 ± 27.4</td>
<td>146.5 ± 28.9</td>
</tr>
<tr>
<td>1 h</td>
<td>331.4 ± 82.4</td>
<td>239.6 ± 76.1*</td>
<td>124.9 ± 24.4</td>
<td>93.8 ± 25.3*</td>
</tr>
<tr>
<td>24 h</td>
<td>340.7 ± 78.7</td>
<td>211.1 ± 52.3*</td>
<td>141.9 ± 37.3</td>
<td>92.8 ± 12.9*</td>
</tr>
<tr>
<td>48 h</td>
<td>315.9 ± 94.6</td>
<td>275.7 ± 70.2</td>
<td>137.4 ± 17.0</td>
<td>100.4 ± 23.1*</td>
</tr>
<tr>
<td>72 h</td>
<td>313.1 ± 82.1</td>
<td>300.1 ± 115.6</td>
<td>130.7 ± 22.3</td>
<td>118.1 ± 38.9</td>
</tr>
</tbody>
</table>

Note: one-way ANOVA test, $p = 0.05$ (cortical RBF) and $p = 0.00$ (medullary RBF) in iopamidol group; $p = NS$ in saline group. *$p < 0.05$, post-injection RBF value vs baseline with least significant difference (LSD) test.
(LSD-test, \( p = 0.04 \) and \( p = 0.01 \), respectively, vs baseline), and gradually returned to a relatively baseline level from 48 to 72 h (\( p = \text{NS} \) vs baseline) after iopamidol-370 administration. The outer medullary RBF was prominently reduced at 1, 24 and 48 h after iopamidol-370 administration (LSD-test, \( p = 0.00 \), \( p = 0.00 \) and \( p = 0.01 \), respectively, vs baseline), but retained at a low level until 72 h after iopamidol-370 administration (\( p = 0.05 \) vs baseline). There was no significant change in either cortical or outer medullary RBF at each time point in the control group. Figure 5 shows the mean change and the percentage of reduction in RBF following iopamidol-370 administration in different time frames. It shows that iopamidol-370 produced a greater reduction in the outer medullary RBF than cortical RBF, which implied a greater vulnerability of the renal medulla to CM-associated ischemia.

Table 2 summarizes the oxygen response of CO, OS, IS and IM to the iopamidol-370 and saline administration. Within the kidney IS, the mean \( R_2^* \) was greatly increased at 1 h after iopamidol-370 administration (LSD-test, \( p = 0.00 \) vs baseline), remained higher than baseline at 24 h (LSD-test, \( p = 0.05 \) vs baseline), and gradually recovered to baseline within 48–72 h after iopamidol-370 administration (LSD-test, \( p = \text{NS} \) vs baseline; Fig. 6). The iopamidol did not produce statistically significant changes in \( R_2^* \) within the kidney CO, OS and IM (LSD-test, \( p = \text{NS} \) vs baseline). In the control group, there was no significant change in \( R_2^* \) in each kidney structure owing to saline injection (LSD-test, \( p = \text{NS} \) vs baseline).

Figure 7 illustrates a serial effect of iopamidol-370 on the renal perfusion and oxygenation within the different anatomic compartments. Shown are five pairs of RBF vs \( R_2^* \) images obtained at 24 h before and 1, 24, 48 and 72 h after iopamidol-370 injection. There is evidence of a prominent hypoperfusion combining with low oxygen level in the renal tissue that reacts to iopamidol-370 administration. Figure 8 shows the serial perfusion and BOLD images from a saline-treated rabbit. It demonstrates that RBF and \( R_2^* \) over time were scarcely changed owing to saline administration.

4. DISCUSSION

Evaluation of the effect of iodinated CM on kidney hemodynamics and oxygenation is critical to better understand and prevent CIN. By applying noninvasive ASL and BOLD MR techniques, the present study has demonstrated that nonionic, high-osmolality iopamidol produces a relatively long-term reduction in kidney function, particularly within the inner stripe of the outer medulla.

The application of ASL and BOLD MRI in abdominal organs is challenging owing to respiration, peristalsis and magnetic susceptibility artifacts. By using a binder secured to control respiratory movements, we were able to obtain images free of motion artifacts. As previously reported, our results show that RBF and oxygenation can be reliably measured by means of ASL and BOLD-MRI. The mean value of baseline RBF in this study is

![Figure 5](image-url). Mean change and the percentage of reduction in RBF within 72 h following iopamidol administration. The mean cortical RBF decreased by 1 h, reached its minimum by 24 h and gradually returned to baseline by 48 h; the medullary RBF decreased to its minimum by 24 h and remained lower than baseline at 72 h (a). Iopamidol produced a greater reduction in RBF within the medulla as compared with the cortex of this kidney (b).

| Table 2. \( R_2^* \) changes following iopamidol-370 and saline administration (means ± SD; Hz) |
|---------------------------------|------------------|---------|---|---------|-------------|---------|
| Time                           | CO                | OS      | IS       | IM         | CO              | OS      | IS       | IM         |
| Baseline                       | 24.4 ± 2.9        | 26.8 ± 4.7 | 34.1 ± 6.4 | 13.1 ± 2.9 | 24.8 ± 2.7       | 26.1 ± 4.9 | 34.3 ± 5.5 | 16.4 ± 4.7 |
| 1 h                            | 24.6 ± 2.3        | 25.5 ± 4.1 | 31.9 ± 5.5 | 14.8 ± 2.7 | 27.1 ± 6.9       | 31.6 ± 6.1 | 49.9 ± 7.3* | 22.3 ± 5.7 |
| 24 h                           | 23.9 ± 3.2        | 27.3 ± 1.6 | 29.8 ± 9.6 | 18.0 ± 4.1 | 25.6 ± 7.6       | 31.6 ± 9.2 | 40.2 ± 7.6* | 17.2 ± 3.8 |
| 48 h                           | 25.1 ± 2.8        | 28.1 ± 2.4 | 31.8 ± 10.9 | 16.4 ± 4.7 | 26.2 ± 8.2       | 31.1 ± 6.7 | 36.9 ± 7.3 | 18.5 ± 4.3 |
| 72 h                           | 25.0 ± 2.6        | 26.8 ± 2.8 | 34.3 ± 3.7 | 17.4 ± 3.3 | 23.1 ± 3.5       | 27.7 ± 4.5 | 36.3 ± 5.9 | 17.1 ± 4.3 |

Note: one-way ANOVA test, \( p = 0.00 \) (IS) and \( p = \text{NS} \) (CO, OS and IM) in iopamidol group; \( p = \text{NS} \) (CO, OS, IS and IM) in saline group. \( *p < 0.05 \), post-injection \( R_2^* \) value vs baseline with LSD test.
consistent with those recently reported by Winter et al. (19). The obtained kidney $R_2^*$ also showed a good accordance with previously established values, as evaluated by the similar BOLD technique (20). However, the accuracy and stability of ASL and BOLD MRI for the measurements of RBF and renal oxygenation depend on different factors, mainly concerning the intrinsic variability of blood pressure, blood oxygenation levels, blood volume, hematocrit and tissue water content. Thus, an adequate imaging strategy is crucial. We acquired at least three consecutive RBF and $R_2^*$ maps within 1 h per day for 3 days in three healthy rabbits before the experiment. Variation in both mean RBF and $R_2^*$ between each subject over time was small, implying that a single FAIR-ASL and BOLD measure is reliable.

4.1. Hemodynamic effects of iodinated CM

It is well known that iodinated CM induces short-term (i.e. over 1 h) renal hemodynamic disturbances that may in part explain CM-related renal injury (21,22). Our study has demonstrated that the effects of CM on kidney function may last for more than 24 h. The hemodynamic effects of iodinated CM on cortical or global RBF are conflicting and difficult to reconcile (12,23). Our study revealed a prominent decrease in cortical RBF owing to iopamidol injection. We ascribe it to experimental models, animal species, dosage of CM used and its physicochemical properties. In addition, FAIR-ASL used in this study is a flow-sensitive sequence, the signal of which depends on blood flow not only in arteries but also in veins. Thus, a persistent stasis-state of venous blood cells owing to iodinated CM (23) will probably decrease the ASL-RBF over a longer time period.

Iodinated CM had a greater effect on renal hemodynamics within the outer medulla as compared with the cortex. The outer medullary RBF was reduced by 37.8% at 24 h, and remained at a low level until 72 h following iopamidol injection. This can be explained by several possible mechanisms: firstly, unique to the kidney is the highly specialized angioarchitecture, in which the

![Figure 6](image_url)

Figure 6. Mean change and the percentage of increase in renal $R_2^*$ within 72 h following iopamidol administration. The mean $R_2^*$ in the kidney IS rapidly arrived at the peak by 1 h (least significant difference test, $p = 0.00$ vs baseline), and remained higher level than the baseline by 24 h ($p = 0.05$ vs baseline), but returned to baseline by 48–72 h; the mean $R_2^*$ in the kidney CO, OS and IM were slightly increased, but the changes did not reach statistical significance ($p = NS$ vs baseline) (a). Iopamidol produced a greater increase in $R_2^*$ within the IS as compared with the CO, OS and IM of this kidney (b).

![Figure 7](image_url)

Figure 7. Serial changes in blood perfusion and oxygenation in the left kidney of a single rabbit owing to iopamidol administration. The cortical RBF was prominently decreased by 1 and 24 h, but gradually improved by 48 and 72 h; the medullary RBF was extremely decreased at 1 h (white arrow), but scarcely improved until 72 h following iopamidol injection (a). $R_2^*$ within the IS remarkably was increased at 1 h (black arrow), but slowly improved in the following 72 h (b).
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da are very long and extremely narrow (24). Only 10% of kidney blood flow directly transflux through this region (25), implying that the medulla even during normal conditions functions at the brink of ischemia. Secondly, CM might cause direct renal vasoconstriction, which is probably caused by the disturbances in several vasoactive mediator systems, e.g. nitric oxide (26), endothelin (27) and adenosine (28). This can well explain the short-term vasoconstriction of most vascular beds, but seems to make no sense for the clarification of longer-term hypoperfusion, since the hemodynamic effects of these vasoactive substances are transient. Thus, other mechanisms are proposed: as hyperosmolar compounds, iopamidol-370 acts as an osmotic diuretic, freely filtered by the glomeruli and poorly absorbed by the renal tubule; the CM with high concentration causes a pronounced osmotic diuresis that distends the tubules and collecting ducts, leading to renal swelling and an increase in intra-renal venous pressure (29); the passive compression of the vessels arising from renal swelling could contribute to the decreased outer medullary RBF; also, the stasis-state of blood cells in the medullary vessels (30,31) partially caused by increased intra-renal venous pressure contributes to the delayed decrease in outer medullary perfusion. Although the half-life period of most iodinated CM is approximately 2–7 h (32) and more than 90% will be cleared from kidney within 24 h after injection, the CM-induced tissue swelling and corresponding increase in intra-renal venous pressure will last for a relatively longer time period. Moreover, the delayed hypo-perfusion found in this study could correspond to the important clinical issue that serum creatinine (Scr) levels of these patients with CIN commonly arrive at a peak within 2–5 days after CM administration (17).

4.2. Effects of iodinated CM on renal oxygenation

BOLD imaging is sensitive to changes in tissue oxygenation and is based on the fact that oxyhemoglobin is diamagnetic, whereas deoxyhemoglobin is paramagnetic. Elevation in deoxyhemoglobin content therefore causes an increase in $R_2^*$, the so-called BOLD contrast. It has been found that the value of $R_2^*$ inversely correlates with the tissue content of oxygen (33), meaning that an increased $R_2^*$ implies a reduction in the oxyhemoglobin content, which subsequently results in a proportional decrease in tissue pO$_2$. Prasad initially employed the BOLD imaging to investigate effects of iodinated CM on renal oxygenation (14). Their study showed that renal medullary $R_2^*$ in rats was increased by inhibition of the synthesis of prostaglandins and nitric oxide, as well as by intravenous injection of iodinated CM, hyperosmotic sodium iothalamate. Moreover, they detected a transient decrease in medullary $R_2^*$ values immediately following the CM administration. The reason for this transient increase in medullary pO$_2$ was not quite clear. They attributed it to a consequence of sudden expansion of the blood volume and perhaps osmotic diuresis. Using a similar BOLD technique, we also detected a dominant decrease in blood oxygen level in outer medullary kidney. Moreover, we made some improvements as compared with Prasad’s study: firstly, a control group was set up in our study; secondly, with the benefit of high strength field to enhance BOLD contrast and SNR, our images provided an ability to identify the signal contrast between different compartments of the kidney. The evident BOLD contrast may depend not only on the properties of MR protocol but also on distinct pO$_2$ gradients between the structures. Thirdly, the longer-term observations showed that the nonionic, hyperosmotic iopamidol-370 produced an extreme, protracted renal hypoxia, particularly in the inner stripe of the outer medulla.

Several mechanisms for the high vulnerability of the deeper portion of the outer medulla to iodinated CM exposure have been suggested. Firstly, iodinated CM cause direct medullary vasoconstriction, which was shown by previous studies (34,35). Secondly, they might damage oxygen delivery indirectly by inducing red blood cell aggregation as well as a remarkable cessation of intra-renal blood flow, probably owing to their high viscosity (31,36). This damage may be more extreme in iso-osmotic, high-viscosity than in hyper-osmotic, low-viscosity CM (23). Thirdly, as a result of the osmotic effect caused by hyper-osmotic iopamidol, the amount of sodium arriving at the thick ascending limb (mTAL) of the loop of Henle will increase, and in turn enhance the active uptake from mTAL (10), leading to a further increase in oxygen utilization. Although we detected a reversible inhibition of renal oxygenation in this study, whether this deficiency of renal function is recoverable in some patients with kidney insufficiency is still unclear. Further studies will focus on this.

Figure 8. Serial perfusion and BOLD images from a saline-treated rabbit. The saline scarcely produced positive change in either RBF (a) or $R_2^*$ (b) within these different compartments of the kidney.
Our study has some limitations. Even carefully controlled, the obtained ASL and BOLD results over a 4 day period were inevitably affected by different factors, e.g., blood pressure, blood oxygenation levels, blood volume, hematocrit and water content. Secondly, as the signal in ASL experiments mainly comes from the encoded longitudinal magnetization of blood in capillaries perpendicular to the selective plane, the signal difference contributed by the blood component parallel to the selective slice is too weak to be inspected. So in theory, the RBF value obtained was likely affected by different factors, e.g. blood pressure, blood oxygenation levels, blood volume, hematocrit and water content.

Finally, limited by the long time with an IR sequence to measure kidney T1 relaxation, our study had to neglect the effects of iodinated CM on the tissue T1 relaxation. In the end, with regard to BOLD imaging, one big challenge is the artifact arising from magnetic-susceptibility effect. In order to obtain the true BOLD effect of renal capillaries, the examination protocol should be carefully prescribed.

In conclusion, with the use of a noninvasive ASL and BOLD MRI, the present study reveals a prolonged decrease in RBF and oxygen level owing to the nonionic, high-osmolality iopamidol. The finding of extreme and protracted hypoxic state of the inner stripe of the outer medulla in the rabbit kidney could be valuable to understand the pathogenesis of CIN.

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