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Validation of quantitative BOLD MRI measurements in kidney: Application to unilateral ureteral obstruction

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Background. Blood oxygenation level dependent (BOLD) magnetic resonance imaging (MRI) provides a measure of deoxyhemoglobin content and therefore an indirect measure of the partial oxygen pressure (pO_2). The main purpose of this study was to examine the relationship between the apparent relaxation rate ($R2^*$) in the pig kidney by BOLD imaging and renal tissue pO_2 levels measured directly by oxygen-sensitive microelectrodes. Second, BOLD imaging was applied to kidneys in pigs subjected to acute unilateral ureteral obstruction (UUO) to examine whether this condition is associated with changes in intrarenal oxygenation.

Methods. Oxygen-sensitive microelectrodes were inserted in the cortex and medulla of pig kidneys ($N = 6$). Different arterial and intrarenal levels of pO_2 were obtained by stepwise changing the oxygen-to-nitrogen ratio supplied by a respirator. Simultaneous BOLD MRI measurements using an $R2^*$-sensitive Echo Planar Imaging (EPI) sequence were performed on the contralateral kidney. In another group of pigs ($N = 3$) BOLD imaging was performed following 24 hours of UUO.

Results. When the inhaled oxygen fraction was 5% to 70%, $R2^*$ was linearly related to pO_2 levels (cortex $\Delta R2^*/\Delta pO_2 = -1.2\ ms^{-1}kPa^{-1}$, and medulla $\Delta R2^*/\Delta pO2 = -1.7\ ms^{-1}kPa^{-1}$). Twenty-four hours of UUO was associated with an increased $R2^*$ in the cortex and a decreased $R2^*$ in medulla as compared with baseline, which remained augmented after the release of UUO, indicating that pO_2 levels were reduced in the cortex and increased in the medulla during and after release of obstruction.

Conclusion. BOLD MRI provides noninvasive estimates of regional renal oxygen content and our study demonstrates that this technique may provide a useful tool in UUO which is associated with altered renal oxygen consumption.

Key words: blood oxygenation level dependent MRI, obstructive nephropathy, kidney tubules, pigs.

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Blood oxygenation level dependent (BOLD) magnetic resonance imaging (MRI) was in this study applied to experimental conditions, where the underlying physiologic changes suggest altered renal oxygen consumption. The interaction between renal medullary transport of sodium and water and oxygen consumption supports that measurement of partial pressure of oxygen (pO_2) in the kidney is an important parameter when renal function is impaired. Precise methods for regional measurements of pO_2 in the renal tissue involve direct insertion of oxygen sensitive microelectrodes, whereas techniques such as near-infrared spectroscopy, nuclear magnetic resonance spectroscopy, and electron paramagnetic resonance allow indirect measurement of the in vivo concentrations of oxygen [1–6]. However, different restrictions and physical requirements make these methods currently unavailable for clinical purposes. BOLD MRI is another noninvasive technique, which has shown capable of providing indirect measures of the renal oxygen content in vivo [7]. This technique is based on diamagnetic properties of oxyhemoglobin whereas deoxyhemoglobin has paramagnetic properties in a magnetic field [8]. Changes in deoxyhemoglobin concentration involve generation of phase incoherence of magnetic spins, leading to signal attenuation in gradient echo sequences and an increase in the apparent spin-spin relaxation rate denoted as $R2^*$. This behavior, combined with the fact that pO_2 in blood is in equilibrium with pO_2 in tissue, potentates BOLD MRI to be an attractive tool for high resolution mapping of the intrarenal oxygenation. Unfortunately, the BOLD technique does not allow quantifying pO_2 in a tissue directly. It is, however, generally assumed that the change of $R2^*$ is closely related to the change of pO_2 [7], implying that values of $\Delta R2^*$ can be interpreted as measures of ΔpO_2 if conversion constants are known; although intrinsically dependent on renal blood flow and renal blood volume.

In the kidney the majority of the renal energy expenditure, estimated from its oxygen consumption, is devoted to the reabsorption of electrolytes filtered into the

tubules. Thus, the local oxygen tension within the kidney tissue reflects the balance between oxygen delivery and consumption of oxygen in viable cells and tissue. The renal medulla has a relatively small blood flow to support the active work of sodium transport via the activity of basolateral sodium, potassium-adenosine triphosphatase (Na^+, K^+-ATPase), and since the renal oxygen consumption has been shown to linearly correlate with the sodium transport [9], lack of oxygen obviously affects this function critically. In view of this fact, it is interesting that the renal medulla exists on the edge of hypoxia [10]. Although the cortical pO_2 has consistently been shown to be higher than that in the medulla [11], the renal cortex may also be susceptible to hypoxia since the cortex is unable to extract sufficient oxygen unless the concentration of oxygen is relatively high [12].

Unilateral ureteral obstruction (UUO) is well-known to be associated with reductions in renal blood flow (RBF), glomerular filtration rate (GFR) and pO_2 in the renal parenchyma, providing the basis for development of obstructive nephropathy [13]. In parallel, renal handling of water and solutes is compromised, leading to impaired urinary concentrating capacity [13]. These metabolic and hemodynamic changes may in part be explained by alterations in the expression of renal prostaglandins and activation of the intrarenal renin-angiotensin system [14–17]. The renin-angiotensin-aldosterone system has been demonstrated to play a critical role in the regulation of sodium and water metabolism through a variety of physiologic pathways. In addition to the hemodynamic effects, angiotensin II may have direct effects on sodium transport in the proximal tubule [18, 19]. Thus, a better understanding of the changes in renal oxygen content during and after release of obstruction may provide a useful avenue to determine when obstruction of the ureter impairs renal functions.

The purposes of the present feasibility study were threefold. First, the relationship between $\Delta R2^*$ measured by BOLD MRI and ΔpO_2 measured by oxygen-sensitive microelectrodes was investigated. Second, BOLD MRI was performed following administration of furosemide to investigate the effect of loop diuretics on the renal tissue oxygenation. Third, BOLD MRI was performed during and after release of UUO to examine whether changes in intrarenal oxygenation associated with this condition can be detected.

METHODS

Animal handling

Twelve female Danish Landrace pigs were included in the study. The animals were kept on a standard pig diet and had free access to food and water until the start of the experiment. The pigs were preanesthetized using 10 mg/kg ketaminol (Veterinaria, Zurich, Switzerland) and 5 mg/kg dormicum (Dumex-Alpharma, Oslo, Norway). Following orotracheal intubation, general anesthesia was maintained with 1.2% isoflurane during surgical procedures. During MRI, anesthesia was accomplished by intravenously infusion of dormicum (5 μg/min/kg), ketaminol (0.3 mg/min/kg), and pancurone (2.5 μg/min/kg) (Organon Teknika, Boxtel, The Netherlands). A dedicated MRI-compatible respirator supplied with two gas flasks containing 100% O_2 and 100% N_2, respectively, maintained artificial ventilation. Each pig received 0.1 mL/min/kg of isotonic saline intravenously throughout the study. Animals were divided into the following protocols.

Protocol 1: Relationship between $R2^*$ and pO_2 in renal tissue ($N = 6$). A catheter was inserted in a femoral artery to allow blood sampling for arterial pO_2 monitoring. One kidney was exposed retroperitoneally by a deep flank incision and immobilized by attaching the peritoneum to the flank with sutures. Oxygen-sensitive microelectrodes were inserted and placed in the central cortical and medullary regions of the kidney guided directly from the measured pO_2 level (i.e., a high pO_2 level indicated that the microelectrode was in the renal cortex and a low pO_2 level indicated that the tip of the microelectrode was in the renal medulla). The body temperature was maintained by surrounding the body with insulating blankets. During the experimental procedure, different arterial and intrarenal levels of pO_2 were achieved by sequentially changing the percentage of the respirator supplied oxygen-nitrogen fraction. The arterial pO_2 levels in the blood samples were analyzed (ABL555) (Radiometer, Copenhagen, Denmark). A decrease in the supply of O_2 may consequently reduce the concentration of saturated hemoglobin. Each pig was subjected to four to five different levels of oxygen concentrations, and the range of O_2 was adjusted from a normoxic/hyperoxic level (O_2 = 70%) to a hypoxic level (O_2 = 5%). All adjustments in the O_2 concentrations were made in a descending order and each change in O_2 concentration was followed by a 20-minute period of rest before additional reduction in O_2 concentration. Measurements of pO_2 and BOLD MRI were performed in an interleaved order. To avoid artefacts induced by the oxygen microelectrode, imaging was performed in the opposite kidney with the assumption that the physiologic conditions of the two kidneys were comparable during the time of examination.

Protocol 2: Measurement of $R2^*$ in response to furosemide ($N = 3$). The effect of loop diuretics on the renal oxygenation was investigated by measuring intrarenal $R2^*$ before and after an intravenous bolus (0.5 mg/kg) of furosemide (Hoechst-Roussel Pharmaceuticals, Kansas City, MO, USA).

Protocol 3: Measurement of $R2^*$ in response to UUO and release of UUO ($N = 3$). Twenty-four hours prior to MRI, pigs were operated upon in general anesthesia.