MR measures of renal perfusion, oxygen bioavailability and total renal blood flow in a porcine model: noninvasive regional assessment of renal function

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Abstract

Background. Magnetic resonance imaging (MRI) may be a useful adjunct to current methods of evaluating renal function. MRI is a noninvasive imaging modality that has the ability to evaluate the kidneys regionally, which is lacking in current clinical methods. Other investigators have evaluated renal function with MRI-based measurements, such as with techniques to measure cortical and medullary perfusion, oxygen bioavailability and total renal blood flow (TRBF). However, use of all three techniques simultaneously, and therefore the relationships between these MRI-derived functional parameters, have not been reported previously.

Methods. To evaluate the ability of these MRI techniques to track changes in renal function, we scanned 11 swine during a state of hyperperfusion with acetylcholine and a saline bolus and subsequently scanned during a state of hypoperfusion with the prolonged use of isoflurane anesthesia. For each time point, measurements of perfusion, oxygen bioavailability and TRBF were acquired. Measurements of perfusion and oxygen bioavailability were compared with measurements of TRBF for all swine across all time points.

Results. Cortical perfusion, cortical oxygen bioavailability, medullary oxygen bioavailability and TRBF significantly increased with the acetylcholine challenge. Cortical perfusion, medullary perfusion, cortical oxygen bioavailability and TRBF significantly decreased during isoflurane anesthesia. Cortical perfusion (Spearman’s correlation coefficient $\rho = 0.68; P < 1 \times 10^{-4}$) and oxygen bioavailability (Spearman’s correlation coefficient $\rho = -0.60; P < 0.0001$) correlated significantly with TRBF, whereas medullary perfusion and oxygen bioavailability did not correlate with TRBF.

Conclusions. Our results demonstrate expected changes given the pharmacologically induced changes in renal function. Maintenance of the medullary oxygen bioavailability in low blood flow states may reflect the autoregulation particular to this region of the kidney. The ability to noninvasively measure all three parameters of kidney function in a single MRI examination and to evaluate the relationships between these functional parameters is potentially useful for evaluating the state of the human kidneys \textit{in situ} in future studies.

Keywords: arterial spin labeling; BOLD; magnetic resonance imaging; swine; total renal blood flow

Introduction

Current methods of evaluating kidney function include measuring serum creatinine, calculating glomerular filtration rate, measuring proteinuria and performing a biopsy. However, these methods cannot evaluate renal function on a regional basis and/or are invasive in nature. A clinical tool that can evaluate renal function noninvasively and on a regional basis would be a useful adjunct to current clinical methods.

Previous studies have evaluated renal function noninvasively using a combination of multiple imaging modalities. Computed tomography (CT) has been used to measure total renal blood flow (TRBF), regional blood flow and the glomerular filtration rate using contrast-enhanced studies [1]; contrast-enhanced ultrasound (US) has been used to study renal blood flow in the renal arteries [2]; magnetic resonance imaging (MRI) has been used to evaluate TRBF, regional perfusion and glomerular filtration rate [3–5]. While the CT measurements of renal function have been well documented in animal studies, the extension to humans in a clinical setting is less certain due to concerns about toxicity due to ionizing radiation and iodinated contrast agents. Additionally, MRI can study changes in intrarenal oxygenation using the blood oxygen level-dependent (BOLD) sequence [6]. However, we are not aware of prior MRI studies that noninvasively measure perfusion and oxygenation.
simultaneously following pharmacological intervention. Studies that use multiple imaging modalities to evaluate renal function are potentially limited by changes and fluctuations in renal status as a result of transporting the subject between scanners during the experiment [5, 7]. It would be useful to evaluate multiple functional parameters of kidney function with a single imaging modality so that renal status remains the same during an experiment.

MRI is a powerful tool that can be used to evaluate multiple functional parameters of kidney function during a single examination. MRI, like CT, provides high spatial resolution and the ability to distinguish the medullary and cortical regions of the kidney. In addition to the ability to measure blood flow and velocity [3, 8–10], MRI can provide physiological information, such as tissue perfusion and oxygen bioavailability [6, 11–15]. Unlike CT, however, MRI does not use ionizing radiation. The multiphase CT exam necessary to assess renal blood flow is associated with a relatively large radiation dose, therefore, making this technique somewhat limited in application to certain patient populations. Furthermore, CT and dynamic MRI techniques for measuring tissue perfusion often rely upon the intravenous injection of contrast agents [16, 17], a potential hazard in patients with renal insufficiency [18, 19]. It would be beneficial to utilize functional MRI techniques that operate independently of contrast agents in patients with renal insufficiency.

MRI measurements of renal artery blood flow, tissue perfusion and oxygen bioavailability can be performed without the use of contrast and during a single imaging session, providing insight into how the kidney functions and how such functional parameters interrelate in vivo. In addition, these MRI techniques have the potential to provide dynamic, sequential measurements of these functional parameters in response to pharmacological or physiological manipulation. However, it remains a difficult challenge to demonstrate the capability of MRI methods to assess dynamic events in the kidney in humans due to the highly invasive nature of pharmacological or physiological manipulations. Due to the similarity of swine renal physiology to humans, a swine model provides a meaningful surrogate for assessing the relationships between perfusion, oxygen bioavailability and TRBF. Previous studies have validated our proposed method for assessing baseline renal tissue perfusion in swine using microspheres as a reference standard [20], have compared MRI-based measurements of oxygen bioavailability with oxygen-sensitive microelectrodes [21] and have demonstrated the accuracy of MRI-based TRBF measurements using phase-contrast (PC) velocity mapping of blood flow [22, 23]. The purpose of this study was to demonstrate the feasibility of MR methods for evaluating regional tissue perfusion, regional oxygen bioavailability and TRBF during physiological and pharmacological interventions in the intact kidney of swine during a single MRI examination.

Materials and methods

Animal protocol

Institutional Animal Care and Use Committee approval was obtained prior to this study. Eleven female swine (34–38 kg, 10–12 weeks of age) were induced with xylazine hydrochloride (2.2 mg/kg) and telazol (7 mg/kg) via intramuscular injection. Swine were intubated with a laryngoscope and maintained with propofol (10 mg/kg/h) and fentanyl (0.0035 mg/kg/h). Hydration was begun with a bolus of 0.9% normal saline and maintained at 15 mL/kg/h. A 6 French catheter was placed in the left femoral artery for intraarterial monitoring of blood pressure, heart rate and SpO2 with a Veris MR monitor system (MEDRAD, INC., Warrendale, PA). A catheter was placed in the supraprenal abdominal aorta via the right femoral artery for the later administration of acetylcholine. Catheter placement was confirmed with angiography. Urine output was measured with a bladder catheter for 9 of 11 swine.

Imaging protocol

An overview of the imaging protocol is displayed in Figure 1. Scans were performed on a standard clinical 1.5 T MR scanner with an eight-element phased array torso coil (Signa HDx, GE Healthcare, Waukesha, WI). To assess oxygen bioavailability, BOLD images were acquired with the following parameters: TR/TE/fip/BW = 87 ms/741.8 ms/40°/±62.5 kHz, FOV = 32–34 cm, NEX = 1.0, slice thickness = 5 mm, 256 × 128 matrix. Three coronal slices were acquired, each during a separate 12-s breath hold. To assess regional tissue perfusion, arterial spin labeling (ASL) perfusion images were acquired in the coronal plane with a balanced steady-state free precession (bSSFP) 2D imaging sequence [24] with the following parameters: TR/TE/fip/BW = 6.6 ms/2.3 ms/70°±41.67 kHz, FOV = 34 cm, NEX = 1.0, slice thickness = 8 mm, 128 × 128 matrix. Nonselective and selective inversion images were alternated until 64 total images (32 pairs) were acquired. For normalization, four proton-density images were acquired with a bSSFP readout without a prior inversion pulse, 2D Fourier-encoded PC images of TRBF were acquired in 8 of the 11 swine with the following parameters: TR/TE/fip/BW = 6.7 ms/3.2 ms/30°/±3.125 kHz, slice thickness = 5 mm, flow encoding in the through plane direction, FOV = 24 × 12 cm2, 14 phases, 256 × 128 matrix.

To assess the MR techniques over a range of renal tissue perfusion levels in each animal, acquisitions were performed at three time points: first during baseline under propofol anesthesia (hereafter ‘baseline’), second after challenge with the renal vasodilator acetylcholine chloride (144 mL/h) administered in the supraprenal abdominal aorta along with a 450 mL bolus of saline (hereafter ‘acetylcholine challenge’) and finally after 2 h of prolonged isoflurane anesthesia (3%) to decrease regional tissue perfusion (hereafter ‘isoflurane delay’, Figure 1). Isoflurane-induced systemic hypotension has the potential to decrease renal perfusion should the blood pressure fall below the autoregulatory zone (~60 mmHg) and if renal cortical vascular resistance is not maintained [25]. After imaging, swine were euthanized with Beuthanasia-d (0.2 mL/kg).

Image and statistical analysis

BOLD images were analyzed with FuncTool® as previously described by Sadowski et al. [15]. Six to 10 Regions of Interest (ROIs) were placed in the cortex and medulla of each kidney; averages were computed from these ROIs separately for the cortical and medullary regions to estimate a mean R2* measurement for each region. ASL perfusion examinations were analyzed with custom scripts written in MATLAB.

![Fig. 1. Timeline demonstrating the acquisition of ASL perfusion, BOLD R2* and PC data during three time points: (i) baseline with the anesthetic propofol, (ii) an acetylcholine challenge with a saline bolus and (iii) during 2 h under the anesthetic isoflurane.](image-url)
Rectangular regions of interest were drawn around each kidney and were registered independently through the image series with automated rigid registration based on normalized mutual information. The registered tag images were averaged and subtracted from the mean, registered control images to obtain a difference image, $D_M$, of the kidney. ASL perfusion was determined based on a one-compartment model below,

$$f = \frac{\lambda}{2\pi \cdot T_1} \frac{\Delta M}{M_0} \cdot \exp\left(\frac{T_1}{T_1}\right)$$  

where $f =$ perfusion, $\lambda =$ tissue-to-blood partition coefficient for water = 80 mL/100 g [26], $x =$ inversion efficiency = 1.0, $T_1 =$ inversion time = 1.2 s and $T_1 =$ longitudinal relaxation time = 1.0 s for the cortex [27]. Each pixel’s measured $\Delta M$ and $M_0$ were used to generate a perfusion map of the entire kidney. Flow values from all the designated cortical pixels were averaged together to provide mean cortical perfusion for each kidney.

PC images were analyzed with CV Flow (Medis, Leiden, The Netherlands) as described by Wentland et al. [23].

Changes in heart rate, mean arterial pressure and urine output between each time point were compared with a paired Student’s $t$-test ($P < 0.05$). Averages of cortical and medullary perfusion and $R_2^*$ were plotted over the three time points. Changes in values of tissue perfusion, $R_2^*$ and TRBF between baseline with propofol and the acetylcholine challenge and between the acetylcholine challenge and the isoflurane delay were evaluated with a paired Student’s $t$-test ($P < 0.05$). Measurements of TRBF versus tissue perfusion, along with measurements of TRBF versus $R_2^*$, across all three time points were plotted and correlated with the Spearman’s correlation coefficient. Measurements of mean arterial pressure were plotted versus TRBF and perfusion. A linear best-fit line was plotted for each set of data and correlated with the Spearman’s correlation coefficient.

### Results

Mean heart rate, mean arterial pressure and mean urine output were 69 beats per minute (b.p.m.), 93 mmHg and 1.8 mL/min, respectively, for the baseline measurement under propofol anesthesia, 78 b.p.m., 93 mmHg and 6.2 mL/min during the acetylcholine challenge and 83 b.p.m., 58 mmHg and 0.5 mL/min after 2 h of delay under isoflurane anesthesia (Table 1). With acetylcholine, the heart rate significantly increased ($P = 0.01$), while the administration of isoflurane did not significantly change the heart rate. There was no significant change in mean arterial pressure with the acetylcholine challenge; however, there was significantly decreased mean arterial pressure with isoflurane ($P < 0.001$). Urine output significantly increased with the acetylcholine challenge ($P = 0.004$) and significantly decreased with the use of isoflurane for 2 h ($P = 0.003$). Typical BOLD $R_2^*$ and ASL perfusion maps are displayed for a single swine in Figures 2 and 3, respectively. Decreased $R_2^*$ relative to baseline was observed during the acetylcholine challenge as indicated by the larger extent of blue coloration in both the cortex and medulla, corresponding to an increase in oxygen bioavailability. Increased $R_2^*$

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HR, heart rate; MAP, mean arterial pressure; UO, urine output; Ach, acetylcholine.

### Table 1. Heart rate (b.p.m.), mean arterial pressure (mmHg) and urine output (mL/min) in swine during the use of the anesthetic propofol, during an acetylcholine challenge with a bolus of 450 cc of saline and finally during 2 h of the anesthetic isoflurane

*Fig. 2.* $R_2^*$ maps during the propofol baseline, the acetylcholine challenge and after 2 h of isoflurane. Areas of blue represent areas of lower $R_2^*$ (increased oxygen bioavailability) and green represents areas of higher $R_2^*$ (decreased oxygen bioavailability). The label C marks a region of interest in the cortex.
relative to baseline was observed during isoflurane delay as indicated by the larger extent of green coloration on the BOLD R2* map, corresponding to a decrease in oxygen bioavailability (Figure 2). ASL images demonstrated an increase in cortical perfusion relative to baseline during the acetylcholine challenge as indicated by the greater extent of red coloration. Tissue perfusion was markedly reduced during isoflurane delay as indicated by the increase in blue coloration on the perfusion maps (Figure 3).

Group-wise comparisons over all 11 swine demonstrated the same pattern depicted in Figures 2 and 3. Specifically, cortical perfusion increased with the acetylcholine challenge (average 200.9 to 267.6 mL/100 g/min; $P < 1 \times 10^{-5}$), while it decreased (average 267.6 to 83.5 mL/100 g/min; $P < 1 \times 10^{-9}$) after the isoflurane delay (Figure 4A). However, medullary perfusion did not demonstrate significant changes with the acetylcholine challenge (average 46.0 to 48.4 mL/100 g/min; $P = 0.59$); medullary perfusion significantly decreased with isoflurane (average 48.4 to 31.1 mL/100 g/min; $P = 0.011$; Figure 4B). Cortical R2* decreased with the acetylcholine challenge (average 10.0 to 8.9/s; $P = 0.019$) and increased with isoflurane (average 8.9 to 11.8/s; $P < 0.0001$; Figure 5A). Medullary R2* decreased with the acetylcholine challenge (average 14.2 to 10.3/s; $P < 0.001$) and increased slightly with isoflurane (average 10.3 to 11.5/s; $P = 0.11$; Figure 5B). TRBF increased with the acetylcholine challenge (average 261.5 ± 93.6 to 475.3 ± 236.9 mL/min; $P = 0.0006$) and decreased after 2 h of isoflurane (average 475.3 ± 236.9 to 88.0 ± 31.7 mL/min; $P < 1 \times 10^{-5}$).

![Fig. 3. ASL perfusion maps during the propofol baseline, the acetylcholine challenge and after 2 h of isoflurane. Blue represents areas of lower tissue perfusion and red represents areas of higher tissue perfusion.](image)

![Fig. 4. Tissue perfusion (mL/100 g/min) in the cortex (A) and medulla (B) during the propofol baseline, the acetylcholine challenge and after 2 h of isoflurane. Error bars represent SD.](image)

![Fig. 5. R2* (per second) measurements in the cortex (A) and medulla (B) during the propofol baseline, the acetylcholine challenge and after 2 h of isoflurane. Error bars represent SD.](image)
TRBF and cortical ASL perfusion demonstrated a positive correlation across all time points in both kidneys (Figure 6A; Spearman’s correlation coefficient = 0.68; P < 1 × 10⁻⁶). However, medullary perfusion did not correlate with TRBF (Figure 6B). TRBF and cortical R2* measurements demonstrated a negative correlation across all time points (Figure 7A; Spearman’s correlation coefficient = -0.60; P < 0.0001). TRBF and medullary R2* measurements also demonstrated a negative correlation, but this trend was not statistically significant (Figure 7B; Spearman’s correlation coefficient = -0.20; P = 0.23). TRBF increased with higher mean arterial pressure (Figure 8A; Spearman’s correlation coefficient = 0.44; P = 0.002). Cortical perfusion demonstrated a positive correlation with mean arterial pressure (Figure 8B; Spearman’s correlation coefficient = 0.54; P < 1 × 10⁻⁵). In contrast, medullary perfusion weakly correlated with mean arterial pressure (Figure 8B; Spearman’s correlation coefficient = 0.26; P = 0.04).

**Discussion**

In this study, the evaluation of TRBF, tissue perfusion and oxygen bioavailability was performed within a single MR examination using a swine model during various physiological and pharmacological challenges. TRBF was compared to changes in tissue perfusion and oxygen bioavailability during baseline, hyper- and hypoperfusion states. In this study, we demonstrated that an acetylcholine challenge caused a significant increase in cortical perfusion and TRBF, whereas the prolonged use of isoflurane caused a decrease in cortical and medullary perfusion and TRBF. While tissue perfusion increased, R2* decreased in both the cortex and medulla, suggesting cortical and medullary oxygen bioavailability increased with the acetylcholine challenge. Conversely, as tissue perfusion decreased, cortical R2* increased suggesting cortical oxygen bioavailability decreased significantly with the prolonged use of isoflurane. Medullary R2* was maintained in the induced low blood flow state. Additionally, TRBF correlated with cortical perfusion and negatively correlated with cortical R2*. TRBF did not correlate with medullary perfusion or R2*. TRBF and cortical and medullary perfusion correlated positively with mean arterial pressure.

Acetylcholine has a short half-life as a result of rapid degradation by acetylcholinesterase. In this study, acetylcholine was administered immediately superior to the renal arteries with the goal of affecting only the local...
renal vasculature. Acetylcholine did not appear to affect the vasculature outside of the region of administration, accounting for the stable mean arterial pressure during this time point. During the isoflurane delay, the anesthetic acted systemically to decrease blood pressure, as demonstrated by the significant drop in mean arterial pressure in Table 1. The drop in blood pressure resulted in decreased TRBF, regional perfusion and cortical oxygen bioavailability as measured by our experiments. There was no significant change in medullary oxygen bioavailability with a drop in blood pressure, likely due to the ability of the medulla to maintain oxygenation in a state of low perfusion [14].

Other investigators have demonstrated similar trends in tissue perfusion and TRBF. Badzynska et al. and Krier et al. demonstrated significantly increased cortical and medullary perfusion following the administration of acetylcholine with the use of perfusion probes and CT, respectively [28, 29], whereas Hartman et al. [25] demonstrated that the volatile anesthetics, including isoflurane, cause a decrease in renal perfusion as measured with radioactive microspheres. Additionally, Gelman et al. [30] used microspheres to demonstrate that renal perfusion decreases with increasing concentrations of isoflurane. Badzynska et al. [28] demonstrated that the intrarenal infusion of acetylcholine increases TRBF with Doppler US, while Chou et al. [31] demonstrated decreased renal plasma flow with the use of isoflurane via measurements with paraaminohippuric acid.

The changes seen in cortical R2*, suggesting changes in oxygen bioavailability, are in concordance with previous investigators who performed studies with invasive measurement techniques, such as with laser Doppler probes. Brezis et al. [32] demonstrated that the renal cortex and medulla are regulated independently and that renal hypoperfusion causes a decrease in cortical oxygen, while medullary oxygenation is maintained. The preservation of medullary oxygenation during a state of decreased perfusion was noted to be due to decreased oxygen usage, which was a result of autoregulatory mechanisms in the medulla and the tubuloglomerular feedback mechanisms in the kidney [33, 34]. In our experiment, there was no change in the medullary R2* during isoflurane delay, suggesting no significant changes in the medullary oxygen bioavailability. Given the state of hypoperfusion during this time point, it was possible that the decrease in blood delivery was almost equal to the decrease in oxygen usage in our experiment. The stable medullary R2* measurements during isoflurane, as well as the lack of correlation between TRBF and medullary R2*, reflect the function of the autoregulatory

Fig. 7. Scatter plot of TRBF (mL/min) versus R2* (per second) in the cortex (A) and medulla (B) during the propofol baseline, the acetylcholine challenge and after 2 h of isoflurane. R and P values are computed from a Spearman correlation.
mechanisms to maintain medullary oxygen bioavailability in a state of hypoperfusion. Furthermore, the differential regulation of the cortex and medulla were clearly seen in our experiment. There was correlation between TRBF and both cortical perfusion (Figure 6) and cortical R2* measurements (Figure 7), whereas no significant correlation existed between TRBF and both medullary perfusion and medullary R2* measurements.

Our study had several limitations. The small sample size may have limited the detection of small changes in medullary oxygen bioavailability with isoflurane, if they exist. While our study successfully demonstrated the effects of a state of increased renal blood flow (acetylcholine challenge) and a state of decreased renal blood flow (isoflurane delay), we did not investigate the effects of recovery from the state of decreased renal function. Due to a change in protocol, PC images were only acquired in 8 of the 11 swine. Our hypoperfusion state was subsequent to a state of hyperperfusion. However, acetylcholine is rapidly degraded by acetylcholinesterase and the saline bolus was quickly micturated (Table 1, significantly higher urine output during the ‘Propofol + Ach’ time point). Furthermore, our measurements during isoflurane administration were acquired 2 h after the hyperperfusion state was terminated. Therefore, it is unlikely that the prior hyperperfusion state affected the renal physiology during our measurements under isoflurane anesthesia. Finally, it is difficult to make any conclusions on the autoregulatory nature of the medulla given the scarce number of measurements obtained while the mean arterial pressure was below the autoregulatory range in swine (~60 mmHg).

In summary, we have demonstrated that the MRI evaluation of TRBF, regional tissue perfusion and oxygen bioavailability in a swine model led to expected changes during various physiologic and pharmacologic challenges. Additionally, we investigated the relationships between these functional MRI measurements in the cortex and medulla. As demonstrated in invasive studies and as was shown in this noninvasive study, TRBF affects the blood flow and oxygen bioavailability in the cortex directly, whereas only with an increase in TRBF does the medullary perfusion and oxygen bioavailability react. In the case of hypoperfusion, the medulla maintains a stable level of oxygen bioavailability, likely as a result of autoregulation. Functional MRI allows for the simultaneous assessment of TRBF, tissue perfusion and oxygen bioavailability and can be used to study how these interrelate between the cortex and medulla. The ability to noninvasively measure TRBF, tissue perfusion and oxygen bioavailability during the same examination allows for the evaluation of the interrelationships between these functional parameters and may provide a means by which the human kidney can be studied longitudinally over time.

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Fig. 8. Scatter plot of mean arterial pressure (mmHg) versus TRBF (mL/min) (A) and perfusion (mL/100 g/min) (B). R and P values are computed from a Spearman correlation.
Conflict of interest statement: None declared.

References


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