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Longitudinal assessment of renal perfusion and oxygenation in transplant donor-recipient pairs using ASL and BOLD MRI

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Abstract

Objectives—To assess renal function in kidney transplant recipients and their respective donors over two years using arterial spin labeling (ASL) and blood oxygen level-dependent (BOLD) MRI, and to prospectively evaluate the effect of losartan on functional MRI measures in recipients.

Materials and Methods—The study included 15 matched pairs of renal transplant donors and recipients. ASL and BOLD MRI of the kidneys were performed on donors prior to transplant surgery (baseline) and on both donors and recipients at 3 months, 1 year and 2 years post-transplant. After 3 months, seven of the 15 recipients were prescribed 25–50 mg/day losartan for the remainder of the study. A linear mixed-effects model was used to evaluate perfusion, R_2^* , estimated glomerular filtration rate (eGFR), and fractional excretion of sodium (FE_{Na}) for changes across time or associated with losartan treatment.

Results—In donors, cortical perfusion in the remaining kidney decreased by 50 ± 19 ml/min/100g (11.8%) between baseline and 2 years ($P < 0.05$), while cortical R_2^* declined modestly by 0.7 ± 0.3 s⁻¹ (5.6%; $P < 0.05$). In transplanted kidneys, cortical perfusion decreased markedly by 141 ± 21 ml/min/100g (34.2%) between baseline and 2 years ($P < 0.001$), while medullary R_2^* declined by 1.5 ± 0.8 s⁻¹ (8.3%; $P = 0.06$). Single-kidney eGFR increased between baseline and 2 years by 17.7 ± 2.7 ml/min/1.73m² (40.3%; $P < 0.0001$) in donors and to 14.6 ± 4.3 ml/min/1.73m² (33.3%; $P < 0.01$) in recipients. Cortical perfusion at 1 and 2 years in recipients receiving 25–50 mg/day losartan was 62 ± 24 ml/min/100g higher than recipients not receiving the drug ($P < 0.05$). No significant effects of losartan were observed for any other markers of renal function.

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Conclusions—The results suggest an important role for non-invasive functional monitoring with ASL and BOLD MRI in kidney transplant recipients and donors, and they indicate a potentially beneficial effect of losartan in recipients.

Keywords

Kidney function; Kidney transplant; Arterial spin labeling MRI; Blood oxygen level-dependent MRI

Introduction

Renal transplantation is considered the best treatment for end-stage renal disease (ESRD) in terms of both outcomes¹ and cost². However, the long-term health risks for both transplant recipients and living donors remain an area of ongoing research. Donors experience reduced renal function along with an increased risk of proteinuria³ and hypertension⁴; however, studies differ as to whether kidney donation is associated with increased long-term risk of cardiovascular disease, ESRD, or mortality^{5–9}. For transplant recipients the major long-term risk is allograft failure, with the majority failing before the end of a recipient's lifetime¹⁰. Longitudinal monitoring of renal function in both transplant donors and recipients may lead to earlier diagnosis of complications and improved long-term outcomes.

Arterial spin labeling (ASL) and blood oxygen level-dependent (BOLD) MRI are noninvasive approaches for assessing renal function which are well-suited for repeated longitudinal use. ASL MRI provides a quantitative measure of perfusion without the use of an exogenous contrast agent^{11,12}. This approach involves acquisition of two images: the “control” image in which the kidney has the same magnetization as blood plasma arriving via perfusion, and the “tag” image in which the magnetization of the kidney is inverted relative to the blood plasma. Perfusion is calculated based on the differential effect of the arriving blood plasma on the total magnetization between the control and tag images. ASL perfusion measurements in the kidney have been previously validated against perfusion measured by microspheres in swine¹³.

BOLD MRI is used to semi-quantitatively evaluate local oxygenation within the kidney¹⁴. Because deoxygenated hemoglobin is paramagnetic, a decrease in oxygen partial pressure (pO_2) and hemoglobin saturation in the blood results in increased local dephasing of the MR signal, expressed as R_2^* ($=1/T_2^*$). Therefore R_2^* may serve as a surrogate for local pO_2 . Although R_2^* can be influenced by additional factors besides oxygenation, R_2^* has shown a close correlation with pO_2 directly measured by invasive microelectrodes and fiber optic probes^{15–20}.

Renal ASL and BOLD MR measures have shown good reproducibility in healthy subjects^{21–25}, transplant recipients^{26–28}, and patients with chronic kidney disease (CKD)²³. Cross-sectional studies with BOLD MRI have shown a significantly lower medullary R_2^* in allografts undergoing acute rejection compared to healthy controls and allografts with acute tubular necrosis^{29,30}. In addition, significantly lower R_2^* in both cortex and medulla has been observed in patients with chronic allograft nephropathy compared to healthy volunteers³¹. Most recently, a large study among transplant recipients showed a significant

relationship between cortical ASL perfusion and CKD stage³². Despite these promising results, there have been few longitudinal studies of allograft function using BOLD MRI^{33,34}, and, to the best of our knowledge, no such studies combining ASL and BOLD MRI.

Non-invasive methods such as MRI may also be used to assess the efficacy of preventive or therapeutic intervention. Blockade of the renin-angiotensin system (RAS) by angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers has shown effectiveness in delaying CKD in non-transplant patients (see Berl³⁵ and Hoogwerf³⁶ for reviews). Although RAS blockade is effective in transplant recipients for management of hypertension, the potential renoprotective effects in this population have not been adequately investigated. ASL and BOLD MRI provide a unique approach for evaluating the effects of RAS blockade on allograft function.

The purpose of this study was twofold. The first was to longitudinally evaluate transplant recipients and their respective donors with ASL and BOLD MRI over two years for changes in renal perfusion or oxygenation. The second was to prospectively evaluate the effects of losartan, an angiotensin II type 1 (AT₁) receptor antagonist, on our MRI measures of renal function in recipients.

Materials and Methods

Study Population

This study was conducted in accordance with the Health Insurance Portability and Accountability Act regulations and was approved by our institution's human patient review board. Fifteen adult kidney transplant recipients (3 women, ages 43, 50 and 56 years; 12 men, age 45.9 ± 10.5 years [mean $\pm$ standard deviation]) and 15 corresponding donors (11 women, age 43.6 ± 12.0 years; 4 men, 44.0 ± 12.5 years) were included. The donor's left kidney was transplanted for 14 cases, with the right kidney transplanted for the remaining case.

All transplant recipients were prescribed a combination of tacrolimus, prednisone and mycophenolate throughout the study for immunosuppression. Thirteen recipients also took anti-hypertension medication as directed by their physicians. Patients were nil per os from 12 midnight prior to each MRI exam. However, a number of recipients necessarily consumed a small amount of water (4 oz. at most) with medication prior to scanning (6 patients at 3 months, 7 at 1 year, and 5 at 2 years post-transplant surgery). Recipient information, including anti-hypertension medication, is shown in Table 1.

To test the effect of losartan on functional MR measurements, seven randomly chosen recipients were prescribed 25–50 mg/day losartan from 3 months post-surgery until the end of the study (LOS+), with the remaining eight recipients serving as a control group (LOS–). Group assignments were randomized prior to baseline data collection. Study personnel, except the study subjects' physicians and the nurse coordinator, remained blinded to the drug therapy until the study and analysis were completed.

Following each MRI exam, blood and urine samples were collected from each patient. These samples were evaluated for estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease formula and for fractional excretion of sodium (FE_{Na}). Single-kidney eGFR in donors prior to surgery was estimated as one-half of total eGFR for ease of comparison with subsequent time points.

MR Imaging

Figure 1 shows a summary of the imaging schedule. Both kidneys of the donors were scanned one day prior to transplant surgery (baseline), and the kidneys were rescanned in both donors and recipients at approximately 3 months, 1 year and 2 years following surgery. Imaging at 3 months occurred prior to any recipients beginning losartan treatment. Imaging was performed on a 1.5 T MR scanner (Signa HDx, GE Healthcare, Milwaukee, WI) using an eight-element phased array cardiac coil (GE Healthcare) placed on the abdomen (donors) or lower abdomen (recipients) proximate to the kidneys. For all recipients a bag of saline was used to minimize susceptibility artifacts that might interfere with BOLD MRI.

ASL images were acquired for a single slice using a flow-sensitive alternating inversion recovery (FAIR) tagging method and a balanced steady-state free precession readout. Acquisition parameters were as follows: inversion time, 1.2 s; repetition time, 4.6 ms; echo time, 2.3 ms; flip angle, 70°; bandwidth, 83.33 kHz; number of control-tag pairs, 32; field-of-view, 34 cm; in-plane resolution, 2.7 mm; slice thickness, 8 mm; slice-selective inversion thickness, 20 mm; scan time, 6–9 min. A sagittal-oblique plane was chosen in order to exclude major arteries from the slice-selective inversion. Respiratory coaching and triggering were used such that the inversion pulse occurred during expiration and each image was acquired during a brief end-expiration breath hold.

BOLD images were acquired for five slices in the coronal plane during a 16-second breath hold using a multi-gradient-recalled echo sequence with the following parameters: echoes, 16; repetition time, 87 ms; echo time, 7–41.8 ms; flip angle, 40°; bandwidth, 125 kHz; number of averages, 1; field-of-view, 34 cm; in-plane resolution, 1.3 mm; slice thickness, 4.5 mm; slice gap, 5.5 mm.

Image Analysis - ASL

All images were analyzed using custom scripts in MATLAB R2011b (The Mathworks, Natick, MA).

Individual ASL and proton density-weighted (PD) images were cropped and automatically registered to one another based on normalized cross-correlation, followed by manual rigid-body registration if necessary. Images which could not be registered were removed. No images were removed in 77% of ASL exams, and in the remaining exams approximately 10% of images required removal. The remaining images were averaged, producing single control (global inversion), tag (slice-selective inversion), and PD images. Tag images were then manually segmented into cortex, medulla, and renal pelvis/vessels.

Perfusion maps for the cortex and medulla were estimated using a one-compartment model¹¹:

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

where f is the perfusion, λ is the tissue-to-plasma partition coefficient (assumed to be 80 ml/100g¹¹), α is the inversion efficiency (assumed to be unity), TI is the inversion time (1.2 s),

M is the signal difference between tag and control, and M_0 is the signal given by the PD image. We assumed the T_1 of cortex and medulla to be 966 and 1410 ms, respectively³⁷. Voxels with perfusion greater than 1000 ml/min/100g in the cortex, or 300 ml/min/100g in the medulla, were assumed to be outliers and removed²⁷.

Image Analysis - BOLD

R_2^* maps were estimated from the BOLD images by fitting a linear function to the natural logarithm of signal magnitude versus TE for each voxel:

$$\ln S = \ln S_0 - R_2^* \cdot TE$$

Here, S and S_0 represent the raw signal at times TE and zero, respectively, and R_2^* is given by the negative of the slope of the fitted line. It was verified by visual inspection that all echoes had sufficient signal to avoid noise amplification from the natural logarithm operation.

T_2^* -weighted echo images which showed good cortical-medullary contrast were used for placement of regions of interest (ROIs). For each exam, five ROIs each were manually placed on the cortex and medulla, and the weighted average of R_2^* within these ROIs was calculated. Areas with apparent susceptibility artifacts were avoided.

Statistical Analysis

Statistical analysis was performed using R (www.R-project.org). Baseline measurements were evaluated for differences between remaining and transplanted kidneys using a paired t-test, and between the LOS- and LOS+ subsets of transplanted kidneys using a Welch t-test.

Longitudinal data were analyzed by linear mixed-effects modeling using the nlme package in R³⁸. For both donors and recipients, the model included the patient as a random effect and time point as a fixed effect. For recipients, the presence of losartan was added as a second fixed effect. Graphical analysis of the data did not show evidence of a time point $\times$ losartan interaction (not shown), so only main effects were included. Statistical significance was defined as $P < 0.05$, and quantitative results are shown as mean $\pm$ standard error unless otherwise specified.

Results

Typical perfusion and R_2^* maps along with corresponding anatomic images are shown in Figure 2. All participants had clinically stable renal function throughout the study. A total of 113 ASL and 107 BOLD data sets were included in the results out of a possible 120 for each

modality. Seven ASL and BOLD exams were unavailable for analysis due to the patient not returning for follow-up scans (Table 2). An additional 6 BOLD exams were excluded due to significant susceptibility artifacts. Therefore the success rates of image analysis were 94% for ASL and 89% for BOLD.

Table 3 shows the measured values of perfusion, R_2^* , eGFR and FE_{Na} in transplanted kidneys as well as those remaining in the donors. Data are expressed as mean $\pm$ standard deviation. Significant differences were observed between remaining and transplanted kidneys at baseline for both cortical R_2^* ($12.4 \pm 1.0 \text{ s}^{-1}$ vs. $11.6 \pm 1.0 \text{ s}^{-1}$, respectively; $P < 0.01$) and medullary R_2^* ($17.4 \pm 1.5 \text{ s}^{-1}$ vs. $18.1 \pm 1.4 \text{ s}^{-1}$, respectively; $P < 0.05$). No other baseline differences were observed between remaining and transplanted kidneys or between the LOS- and LOS+ transplanted kidneys.

Longitudinal Evaluation of Donors

Model estimates for renal perfusion, R_2^* , eGFR and FE_{Na} in the donors' remaining kidneys are summarized in Table 4. Normalized perfusion and R_2^* values at each time point, relative to baseline, are shown in Figure 3. Perfusion of the renal cortex showed a gradual decline over time (Figure 3a), decreasing by 11.8% between baseline and 2 years (average difference = $-50 \pm 19 \text{ ml/min/100g}$; $P < 0.05$). In addition, R_2^* within the cortex (Figure 3c) decreased by 5.6% between baseline and 1 year ($= -0.7 \pm 0.3 \text{ s}^{-1}$; $P < 0.05$) and remained lower than baseline at 2 years ($P < 0.05$). Over this same period and despite reduced overall cortical perfusion, eGFR increased by 33.0% between baseline and 3 months ($= 14.5 \pm 2.7 \text{ ml/min/1.73m}^2$; $P < 0.0001$) and remained 28.0% and 40.3% higher than baseline at 1 year ($= 12.3 \pm 2.8 \text{ ml/min/1.73m}^2$; $P < 0.0001$) and 2 years ($= 17.7 \pm 2.7 \text{ ml/min/1.73m}^2$; $P < 0.0001$), respectively. Although FE_{Na} increased by 83% between baseline and 3 months ($= 0.5 \pm 0.2 \%$; $P < 0.05$), this parameter recovered thereafter to values similar to baseline. No significant changes in medullary perfusion (Figure 3b) or medullary R_2^* (Figure 3d) were observed in the remaining donor kidneys.

Longitudinal Evaluation of Recipients: Effects of Time Point

Model-estimated functional parameters for the transplanted kidney are summarized in Table 5, with normalized values, relative to baseline, shown in Figure 4. Note that the baseline values refer to the kidney in situ within the donor prior to surgery. Independent of the effects of losartan, cortical perfusion decreased by 24.0% between baseline and 3 months ($= -99 \pm 18 \text{ ml/min/100g}$; $P < 0.001$) in the transplanted kidney (Figure 4a). Furthermore, cortical perfusion was 28.4% and 34.2% less than baseline at 1 year ($= -117 \pm 21 \text{ ml/min/100g}$; $P < 0.001$) and 2 years ($= -141 \pm 21 \text{ ml/min/100g}$; $P < 0.001$) post-transplant, respectively. R_2^* within the medulla (Figure 4d) decreased by 7.7% between baseline and 3 months ($= -1.4 \pm 0.6 \text{ s}^{-1}$; $P < 0.05$) and by 9.4% between baseline and 1 year ($= -1.7 \pm 0.7 \text{ s}^{-1}$; $P < 0.05$). Medullary R_2^* at 2 years ($= -1.5 \pm 0.8 \text{ s}^{-1}$) failed to show statistical significance with respect to baseline, although it should be noted that the P -value of this comparison was 0.06. eGFR increased compared to baseline from 26.4% at 3 months ($= 11.6 \pm 3.6 \text{ ml/min/1.73m}^2$; $P < 0.01$) to 33.3% at 2 years ($= 14.6 \pm 4.3 \text{ ml/min/1.73m}^2$; $P < 0.01$). FE_{Na} increased by 67% between baseline and 3 months ($= 0.4 \pm 0.2 \%$; $P < 0.05$) and 100% between baseline and 1 year ($= 0.6 \pm 0.2 \%$; $P < 0.05$), but returned to baseline values at 2

years. No significant changes in medullary perfusion (Figure 4b) or cortical R_2^* (Figure 4c) were observed.

Longitudinal Evaluation of Recipients: Effects of Losartan

Cortical perfusion in recipients receiving 25–50 mg/day losartan was estimated to be 62 ± 24 ml/min/100g higher than recipients not receiving the drug ($P < 0.05$; Table 5). Note that this estimation is independent of time point and includes measures in recipients at both 1 year and 2 years. This represented a 21.0 – 22.9% difference between LOS– and LOS+ groups. The difference of perfusion between LOS– and LOS+ groups was also equivalent to 44.0 – 53.0% of the amount by which cortical perfusion declined after 1 year in the absence of losartan. No significant effects of losartan were observed for any other markers of renal function.

Discussion

Functional MRI techniques such as ASL and BOLD enable noninvasive assessment of kidney physiology which otherwise may be inaccessible in a clinical setting. In this study progressive decreases in cortical perfusion and R_2^* relative to baseline were shown in both donors and recipients over the 2 year follow-up. We also showed prospectively that low-dose losartan treatment mitigates the loss of cortical perfusion in recipients by approximately half, but does not significantly affect R_2^* .

Donors showed a modest decline of cortical perfusion (11.8%) and cortical R_2^* (5.6%) over the course of the study. Cortical perfusion previously has been estimated to decrease by 1% per year with age in healthy individuals³⁹. While small in magnitude, the average perfusion decrease in this context would suggest a nearly six-fold increase in the rate of decline compared to the general population. With respect to R_2^* , it is difficult to evaluate the functional significance of the observed magnitude of the change in cortical R_2^* because estimates of the relationship between age and renal R_2^* are not available, and because direct calibration of R_2^* against absolute pO_2 in the kidney is difficult in patients. However, we note that there were no significant changes in medullary R_2^* in donors, suggesting medullary function was maintained despite changes in the cortex^{40,41}.

Changes in MR measures in donor kidneys were accompanied by up to a 40.3% increase in single-kidney eGFR. Increased glomerular filtration is a known adaptation to the loss of renal mass in donors following transplant nephrectomy, and the magnitude of increase in eGFR observed in this study corroborates previous reports⁴². However, these changes in glomerular filtration typically have been attributed to increased renal blood flow⁴³. In addition, previous studies in normal volunteers and transplant recipients using ASL MRI have shown a positive correlation between cortical perfusion and eGFR^{27,32}. Our finding in the current study of increased eGFR despite reduced cortical perfusion in the native donor kidneys is therefore surprising. One possible explanation is that hypertrophy of the native kidney results in lower perfusion, because the unit of measurement is normalized to mass, and implicitly volume, of tissue. This is consistent with a recent study in which native donor kidneys following nephrectomy showed an increase in total renal plasma flow but no change in plasma flow per unit mass⁴⁴. Another contribution may be increased vascular resistance

in the efferent arterioles compared to the afferent arterioles. Efferent arterioles have increased sensitivity to several molecules which elicit vasoconstriction, including angiotensin II⁴⁵, atrial natriuretic peptide⁴⁶, and vasopressin⁴⁷. Increased activity of these molecules might explain our findings in donors; however, the specific mechanisms as well as the clinical implications of the moderately decreased cortical perfusion in donors clearly require further investigation.

The observed decline in cortical perfusion (24.0–34.2%) in the transplanted kidneys was more expected. The transplantation procedure is known to subject the allograft to some degree of injury, particularly from ischemia and reperfusion. This may result in nephron loss and, therefore, reduced renal function. In addition, calcineurin inhibitors such as tacrolimus, which was prescribed to all recipients in this study for immunosuppression, are known to produce severe vasoconstriction and reduced renal blood flow. Finally, allograft anastomosis to the iliac artery may have contributed to increased vascular resistance, as the lumen of this artery is much smaller than that of the aorta. We note that the largest reduction of cortical perfusion occurred between baseline and 3 months, while values at later time points were comparatively stable. This suggests that the underlying mechanisms were present soon after transplantation.

Approximately half of the reduction in cortical perfusion for the transplanted kidney at 1 and 2 years was mitigated by a regimen of 25–50 mg/day losartan. Losartan specifically blocks the AT₁ receptor, inhibiting the activity of RAS. Losartan has been shown to reduce vascular resistance of renal arterioles in renal transplant recipients⁴⁸, which may explain the increased cortical perfusion in the LOS+ group. Previous studies have shown renoprotective effects of RAS blockade by losartan, such as reducing proteinuria in diabetic patients and slowing the progression of CKD in non-transplant patients⁴⁹. The current study indicates losartan may provide benefits to allograft recipients as well, and further research of losartan in the context of renal transplantation is warranted.

In transplant recipients, R_2^* decreased over time within the medulla (7.7–9.4%) but not in the cortex. This suggests increased oxygenation of the medulla and is consistent with a previous cross-sectional study showing decreased medullary R_2^* in transplant recipients compared to healthy volunteers²⁶. Similar to our observations of cortical perfusion, medullary R_2^* changed most dramatically between baseline and 3 months and subsequently stabilized at later time points. Notably, losartan had no significant effect on medullary R_2^* , indicating that changes in this parameter were independent of cortical perfusion⁴⁰. Increased oxygenation within the medulla may therefore reflect reduced tubular utilization of oxygen, possibly associated with decreased sodium reabsorption within the thick ascending limb⁵⁰. The observed increase in FE_{Na} in the transplanted kidney also suggests reduced sodium reabsorption, and the absence of response of FE_{Na} to losartan parallels that of medullary R_2^* .

Interestingly, baseline measurements of medullary R_2^* were greater in the transplanted kidney compared to the remaining kidney. This corresponds to a possible difference between R_2^* in the left and right kidneys in the donor, because in 14 of the pairs the left kidney was transplanted. This relationship has been previously observed in healthy volunteers by

Simon-Zoula et al., who attributed it to a spatial limitation contributing to reduced venous flow within the left renal vein and therefore greater deoxyhemoglobin concentration²².

We acknowledge several limitations of the present study. First, clinically significant allograft dysfunction or rejection was not seen in our patient population. Therefore, the relationship between functional MRI measures and clinical outcome is unclear. This is partially a result of the relatively small sample size in this study. Mean differences in functional markers at baseline between LOS– and LOS+ groups, although not significant, are likely also due to small sample size (Table 3). However, we note that the use of patient as a random effect in the model accounted for systematic offsets at baseline. Second, although changes in donor perfusion and R_2^* in this study were statistically significant, their magnitude was small with respect to the repeatability of the methods. Published values of within-subjects coefficient of variation (CV) for cortical ASL perfusion range from 4.8 to 13.1%¹³. For R_2^* , CVs of 4.0% for cortex and 5.2% for medulla have been reported²⁶. Therefore the current sensitivity of the MRI methods may be insufficient for clinical evaluation of donors over periods less than 2 years. This is less of a limitation for transplant recipients, as relatively large changes were observed in this group. Third, both ASL and BOLD MRI are sensitive to respiratory motion and magnetic susceptibility effects. The effects of motion were carefully mitigated through respiratory triggering and coaching and removal of motion-corrupted images when necessary. Susceptibility effects, on the other hand, were especially challenging in the case of transplant recipients due to the location of the allograft. Allografts were anastomosed to the iliac artery and positioned in the lower abdomen. Proximity to bowel gas may cause substantial bulk susceptibility artifacts in recipient BOLD scans, severe enough in some cases to prevent analysis of an exam (Table 2). Fourth, our analysis of the ASL data involved assumed values for T_1 and α . Higher T_1 values have been reported in transplanted compared to native kidneys^{51,52}, and T_1 for both groups is correlated with eGFR⁵². Therefore, this study may have overestimated perfusion for transplanted kidneys. The accuracy of quantitation could be improved by incorporating patient-specific T_1 measurements as well as measured values of α . Fifth, the availability of a higher field strength scanner, such as 3 T, likely would have improved data quality, especially with respect to ASL. The increased T_1 at higher field strength reduces the label decay during the inversion time, resulting in a higher signal-to-noise ratio, improved quantification accuracy, and increased time available for acquiring more slices or higher spatial resolution⁵³. For BOLD MRI, the increased range of R_2^* values at higher field strength may enhance image contrast and improve the precision of R_2^* measurement, although the increased effect of susceptibility artifacts may prove limiting⁵⁴. Finally, the acquisition of ASL and BOLD images in different planes (sagittal and coronal, respectively) precluded the opportunity for regional comparison between the two modalities. The relationship between ASL perfusion and R_2^* may provide additional insight into renal function and disease. A sagittal image slice was necessary for ASL to avoid labeling of the aorta. However, there are in principle no restrictions on the orientation of BOLD images, although BOLD MRI is typically analyzed in the oblique coronal plane. Nonetheless, we recommend that similar multi-parametric studies in the future use a common sagittal slice for all images to enable direct comparison.

In conclusion, this study finds significant long-term changes in several markers of renal function following transplantation in both donors and recipients who are clinically stable. In addition, the reduction in cortical perfusion in recipients is partially reversible by low-dose losartan, but without a consummate change in medullary R_2^* . Although the clinical significance of our results is not yet clear, ASL and BOLD MRI show promise for long-term functional monitoring and may improve management of renal health for both donors and recipients.

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Figure 1. Imaging schedule for donors and recipients. The baseline scan was performed in donors prior to transplant surgery. For the first 3 months no recipients received losartan (LOS-), and after this time point a subset were given the drug for the remainder of the study (LOS+). The left kidney was transplanted in 14 of the 15 pairs.

Figure 2.

Anatomic MR images with corresponding functional maps for a single subject (Donor 11 at 3 months). (a) T₁-weighted ASL tag image in the sagittal plane. (b) ASL perfusion map. (c) T₂*-weighted BOLD image in the coronal plane. (d) R₂* map. Distinct differences between cortex and medulla can be seen in both the perfusion and the R₂* map. Very high values in the central region of the kidney in (b) and (d) are outliers attributable to blood vessels. These regions were excluded from analysis.

Figure 3.

Model estimates of cortical perfusion (a), medullary perfusion (b), cortical R_2^* (c), and medullary R_2^* (d) in donors' remaining native kidneys, normalized to baseline. Cortical perfusion was significantly less than baseline at 2 years, while cortical R_2^* was significantly less than baseline at 1 and 2 years. Error bars indicate standard error of the mean. *: $P < 0.05$ vs. baseline

Figure 4.

Model estimates of cortical perfusion (a), medullary perfusion (b), cortical R_2^* (c), and medullary R_2^* (d) in transplanted kidneys, normalized to baseline. Cortical perfusion was significantly less than baseline at all follow-up time points, independent of losartan. Medullary R_2^* was significantly less than baseline at 3 months and 1 year. Cortical perfusion was significantly greater in the LOS+ group compared to LOS-. Error bars represent standard error of the mean.

*: $P < 0.05$ LOS- vs. baseline

†: $P < 0.05$ LOS- vs. LOS+

Table 1

Recipient demographic information.

Recipient	Gender	Age (years)	BMI (kg/m ²)	Losartan	Anti-hypertension
1	M	57	27.0		Atenolol, Lasix, Hydralazine, Nifedipine
2	M	57	23.2	+	Amlodipine
3	M	35	24.2	+	Amlodipine, Metoprolol
4	M	41	20.0		Propranolol
5	M	60	29.2		None
6	F	43	32.0	+	Amlodipine
7	M	54	28.9		Clonidine, Doxazosin, Metoprolol, Nifedipine
8	F	56	20.2	+	Amlodipine, Metoprolol
9	M	43	30.7	+	Amlodipine, Clonidine, Lasix, Metoprolol
10	M	36	27.5	+	Amlodipine, Metoprolol
11	M	37	29.1		Atenolol, Hydrochlorothiazide
12	M	47	33.2		None
13	M	55	29.4	+	Metoprolol, Norvasc
14	M	29	33.1		Clonazepam, Lisinopril, Nifedipine
15	F	50	22.8	+	Amlodipine

Table 2

Imaging exams excluded from the final results.

Patient	Exam(s)	Time Point(s)	Reason
Donor 1	ASL and BOLD	3 months, 1 year, 2 years	Patient absence
Donor 6	ASL and BOLD	1 year	Patient absence
Donor 15	ASL and BOLD	3 months, 1 year, 2 years	Patient absence
Donor 9	BOLD	2 years	Susceptibility artifacts
Recipient 1	BOLD	2 years	Susceptibility artifacts
Recipient 7	BOLD	1 year, 2 years	Susceptibility artifacts
Recipient 9	BOLD	2 years	Susceptibility artifacts
Recipient 11	BOLD	2 years	Susceptibility artifacts

Table 3

Summary statistics of raw data for the remaining and transplanted (Tx) kidneys.^a

	Baseline			3 Months			1 Year			2 Years			
	Remaining	Tx (All)	Tx (LOS-)	Tx (LOS+)	Remaining	Tx (LOS-)	Tx (LOS+)	Remaining	Tx (LOS-)	Tx (LOS+)	Remaining	Tx (LOS-)	Tx (LOS+)
Perfusion, Cortex ^b	422 (67)	412 (60)	440 (73)	388 (34)	412 (65)	332 (87)	296 (40)	404 (63)	324 (87)	324 (87)	375 (62)	299 (78)	301 (98)
Perfusion, Medulla ^b	47 (34)	41 (30)	34 (20)	48 (39)	28 (26)	45 (41)	32 (18)	32 (23)	36 (22)	30 (15)	44 (29)	26 (24)	31 (14)
R ₂ [*] , Cortex ^c	12.4 (1.0)	11.6 (1.1) **	11.3 (0.7)	12.0 (1.3)	11.9 (1.0)	12.4 (0.9)	11.4 (0.8)	11.6 (0.8)	12.5 (1.2)	11.6 (1.2)	11.6 (1.1)	11.5 (1.1)	12.3 (1.2)
R ₂ [*] , Medulla ^c	17.4 (1.5)	18.1 (1.4) *	18.3 (1.1)	17.9 (1.7)	17.8 (1.3)	17.8 (2.5)	15.7 (1.1)	16.9 (1.9)	17.7 (2.6)	16.1 (3.2)	17.2 (2.0)	17.5 (2.3)	16.3 (1.3)
eGFR ^d	43.9 (7.5)	43.9 (7.5)	47.2 (7.9)	40.9 (6.2)	58.5 (9.2)	49.0 (3.1)	61.1 (13.0)	56.1 (5.8)	52.6 (7.4)	55.4 (14.3)	61.7 (8.9)	56.0 (11.2)	62.0 (20.9)
FENa ^e	0.6 (0.4)	0.6 (0.4)	0.8 (0.4)	0.4 (0.2)	1.1 (0.6)	0.8 (0.6)	1.2 (0.6)	0.8 (0.6)	0.9 (0.3)	1.2 (0.9)	0.7 (0.3)	0.8 (0.5)	0.7 (0.6)

Data are mean values with standard deviation in parentheses.

ml/min/100g

1/s

ml/min/1.73m²; baseline value is listed as 0.5 × (Total eGFR) for comparison with subsequent single-kidney measurements.

%

*P < 0.05;

**P < 0.01 remaining vs. Tx at baseline

Table 4Estimates of model parameters of functional markers for the kidney remaining in the donors.^a

	Baseline (B)	(B → 3 Mo)	(B → 1 Yr)	(B → 2 Yrs)
Perfusion, Cortex ^b	422 (17)	−12 (19)	−23 (19)	−50 (19) *
Perfusion, Medulla ^b	47 (7)	−19 (10)	−15 (11)	−3 (10)
R ₂ [*] , Cortex ^c	12.4 (0.3)	−0.4 (0.3)	−0.7 (0.3) *	−0.7 (0.3) *
R ₂ [*] , Medulla ^c	17.4 (0.4)	0.5 (0.6)	−0.5 (0.6)	−0.1 (0.6)
eGFR ^d	43.9 (2.1)	14.5 (2.7) ****	12.3 (2.8) ****	17.7 (2.7) ****
FE _{Na} ^e	0.6 (0.2)	0.5 (0.2) *	0.2 (0.2)	0.1 (0.2)

^aData are mean values with standard error in parentheses. represents the difference with respect to baseline.^b ml/min/100g^c 1/s^d ml/min/1.73m²; baseline value is listed as $0.5 \times (\text{Total eGFR})$ for comparison with subsequent single-kidney measurements.^e %* $P < 0.05$;**** $P < 0.0001$ vs. baseline

Table 5

Estimates of model parameters of functional markers for the transplanted kidney.^a

	Baseline (B)	(B → 3 Mo)	(B → 1 Yr)	(B → 2 Yrs)	(LOS- → LOS+)
Perfusion, Cortex ^b	412 (19)	-99 (18) ***	-117 (21) ***	-141 (21) ***	62 (24) †
Perfusion, Medulla ^b	41 (7)	-2 (9)	-9 (10)	-14 (10)	3 (10)
R ₂ [*] , Cortex ^c	11.6 (0.3)	0.2 (0.3)	0.2 (0.4)	0.4 (0.4)	0.1 (0.4)
R ₂ [*] , Medulla ^c	18.1 (0.6)	-1.4 (0.6) *	-1.7 (0.7) *	-1.5 (0.8)	0.3 (0.8)
eGFR ^d	43.9 (3.1)	11.6 (3.6) **	9.4 (4.2) *	14.6 (4.3) **	1.6 (4.5)
FE _{Nu} ^e	0.6 (0.2)	0.4 (0.2) *	0.6 (0.2) *	0.2 (0.2)	-0.2 (0.2)

^a Data are mean values with standard error in parentheses. for time points represents the difference with respect to baseline. (LOS- → LOS+) represents the difference between recipient groups and includes both 1 year and 2 years.

^b ml/min/100g

^c 1/s

^d ml/min/1.73m²; baseline value is listed as 0.5 × (Total eGFR) for comparison with subsequent single-kidney measurements.

^e %

* $P < 0.05$;

** $P < 0.01$;

*** $P < 0.001$ LOS- vs. baseline

† $P < 0.05$ LOS- vs. LOS+