DCE-MRI demonstrates immediate post-perfusion microvascular hyperpermeability in the mouse renal cortex following ischemia induced by renal artery clamping.

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Introduction: Upon an ischemic insult, the depletion of energy in renal epithelial cells activates many systems that directly cause disruption of the cytoskeleton and cell polarity, and lead to cell death. Immediately after reperfusion, the hemodynamics of the ischemic area is compromised, as demonstrated by histopathology initially, and by intravital microscopy and other techniques more recently.[1,2,3,4] This so called "no-reflow" phenomenon appears to trigger a cascade of events resulting in tubulointerstitial damage.

Endothelial dysfunction has a major role in the development of renal ischemia-reperfusion (R/I) injury because the release of cytokines and chemokines from endothelial cells potentiates interaction with leukocytes and platelets and compromises microcirculation and the recovery process.[5] In addition, injury to endothelial cells leads to cell swelling and loss of the integrity of endothelial barrier.[6] The endothelial injury is associated with loss of endothelial NO synthase (eNOS) activity and subsequent vasoconstriction.

In this abstract, we describe the use of dynamic contrast enhanced MRI (DCE MRI) using an intravascular contrast agent (Gd-DTPA) conjugated to bovine serum albumin (BSA-GdDTPA), in a mouse R/I model in order to characterize the changes in vascular flow and permeability following reperfusion.

Methods: Unilateral renal ischemia was surgically induced in three male NIH Swiss mice using a nontraumatic microvascular clamp. Briefly, each mouse was anesthetized, the left kidney exposed and decapsulated, and the renal pedicle clamped for 30 minutes. After the clamp was applied, the kidney was repositioned in the renal fossa. The right kidney was not manipulated or clamped and served as an endogenous control within each mouse. The mouse was then positioned in a 4.7 T animal MR scanner, and scout and calibration images obtained to determine the optimal position for renal imaging. After 30 minutes, the clamp was removed, and the mouse replaced in the proper position in the MR scanner. Following an intravenous bolus of BSA-GdDTPA (0.01 mmole/kg) via tail vein injection, 40 minutes of dynamic contrast-enhanced imaging of both kidneys was performed using a spin echo sequence with TR=100ms and TE=7ms. DCE-MRI imaging commenced within 15 minutes after removal of the clamp. A control mouse underwent surgery to expose the right kidney and renal artery without placement of a renal artery clamp. This mouse was imaged in the same fashion as the experimental mice.

Results: Post-contrast T1-weighted images demonstrate enlargement of the reperfused kidney, with significantly greater corticomedullary differentiation compared with the control kidney [Fig. 1]. In the cortex of the clamped and reperfused kidney, there is rapid uptake of contrast to a similar level as the peak uptake in the control kidney. However, in the reperfused kidney there is continued slow rise in enhancement, while in the control kidney there is immediate slow washout of contrast following the initial peak. This results in overall higher peak contrast enhancement in the reperfused cortex compared to that of the control [Fig. 2]. The continued gradual increase in uptake of contrast agent in the reperfused kidney suggests increased capillary permeability leading to slow extravasation of contrast into the renal cortical interstitium after initial delivery of contrast. There is no significant difference in peak enhancement and uptake and washout patterns in the renal medulla of the reperfused and control kidneys [Fig. 2]. In light of the DCE data, the increased size and corticomedullary differentiation of the reperfused kidney is likely due to edema arising from vascular leakage in the cortex.

In the control mouse, there was no discernible difference in contrast uptake patterns between the right and left kidneys. The cortical and medullary contrast uptake curves in the sham surgery mouse were similar to those of the control kidneys in the experimental mice.

Discussion: Conventional small molecule gadolinium-based contrast agents such as Gd-DTPA, are cleared by the kidney via glomerular filtration. Ninety-eight percent of Gd-DTPA is filtered in the renal cortex, and no significant amount is secreted or resorbed by the tubules.[7] Thus, the T1 shortening effects of Gd-DTPA in the renal cortex and medulla are due to a combination of glomerular filtration and capillary perfusion rather than due to perfusion alone. The large size of BSA-GdDTPA (MW ~ 80 kD) precludes glomerular filtration of the contrast agent and prolongs vascular retention. It also precludes leakage of the contrast agent into the interstitium of tissues with normal capillary beds. Thus, leakage of BSA-GdDTPA observed in this model signifies a pathologic increase in vascular permeability.

Dynamic imaging of the mouse kidney with an intravascular contrast agent immediately after reperfusion demonstrates increased vascular permeability in the renal cortex. There is no evidence of similar change in the renal medulla. This may be due to the relative hypovascularity of the renal medulla compared with the cortex, but the exact mechanism is unknown. In addition, the data do not indicate increased blood flow into the reperfused renal cortex. Additional experiments are ongoing to understand the mechanism behind these observations and to evaluate changes in reperfusion in the first 5 minutes following removal of the clamp. However, these initial results suggest that a sustained increased in perfusion of the cortex and medulla does not occur beyond the first few minutes after reperfusion, if at all. In addition to helping to increase our understanding the physiology and biology of renal ischemia and reperfusion, this model will also be useful for testing drugs designed to protect the kidneys during ischemia and reperfusion.

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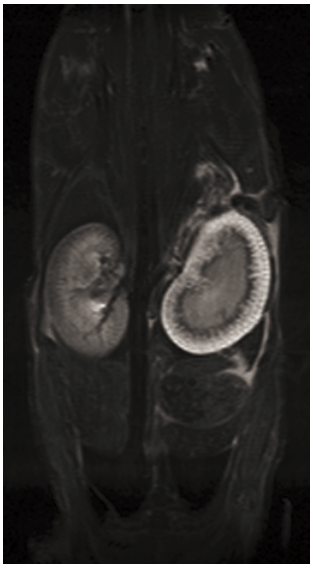

Figure 1: (left) BSA-GdDTPA enhanced MRI image showing the clamped and reperfused (right) and control (left) kidneys in a mouse.

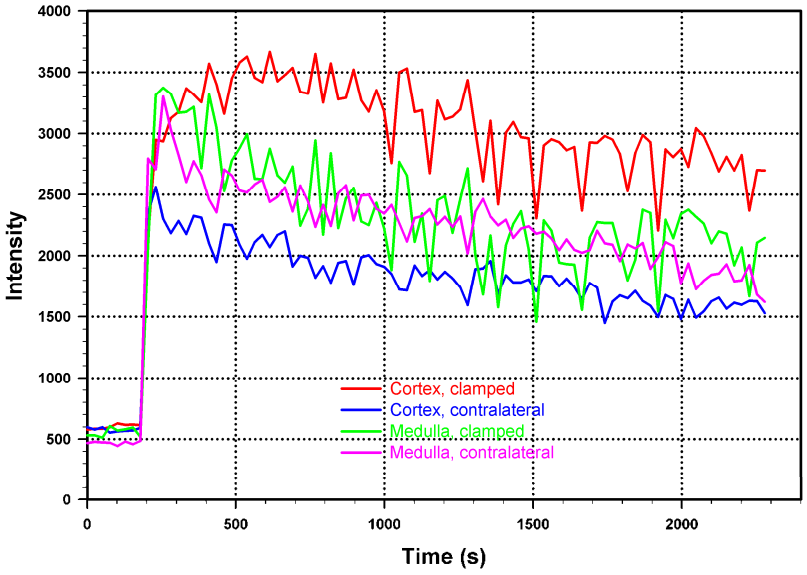

Figure 2: (right) DCE-MRI signal enhancement curves of regions of interest in the kidneys of the mouse depicted in Figure 1.