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Histopathologic Correlates of Irreversible Renal Injury in Renal Artery Stenosis

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Aim: The aim of this study was to define the functional correlates of reversibility following restoration of blood flow in the murine 2K1C model of renovascular hypertension.

Method: Renal artery stenosis surgery (RAS) was performed by placement of a polytetrafluoroethylene cuff on the right renal artery (N=18). Sham surgery was performed without cuff placement (N=6). In two groups the cuff was removed at 7 days (7D cuff-off, N=6) and 14 days (14D cuff-off, N=6) after surgery. In the RAS group, cuff was left in place for 28 days (28D RAS, N=6). Kidneys were harvested at 28 days for assessment of histology and microvessel density (MVD). Renal blood perfusion and oxygenation were measured using 16.4T MRI. Blood pressure measurements were done using tail cuff method.

Results: In 7D cuff-off group, baseline intra-renal perfusion (891±142.8 ml/100g/min) was significantly reduced (311±73.4 ml/100g/min, p<0.0001) following cuff placement. Perfusion was restored to normal level (810±81.2 ml/100g/min) at 28 days following cuff removal at 7 days after RAS. In 14D cuff-off group, baseline intra-renal perfusion (846±74.5 ml/100g/min) was also significantly reduced (304±45.9 ml/100g/min, p=0.0002) following cuff placement with non-significant improvement (579±112.9 ml/100g/min) at 28 days after cuff removal at 14 days after RAS. Baseline intra-renal perfusion (905±54.9 ml/100g/min) in the 28D RAS group was significantly reduced (455±56.4 ml/100g/min, p<0.0034) following cuff placement and the reduction was maintained throughout the study period (478±22.2 ml/100g/min).

7D cuff-off group (142±8.2 mg) showed no significant difference in kidney weights measured at 28 days compared to the sham group (154±4.8 mg), but was significantly higher compared to the 28D RAS group (67±10.5 mg, p=0.0010). The kidney weights of the 14D cuff-off group (86±18.3 mg) measured at 28 days was not significantly different from the 28D RAS group. The 7D cuff-off group had a significantly lower % atrophy (7±2.2%, p=0.0042) and higher MVD count (152±6.5, p=0.0045) compared to 28D RAS group (% atrophy 66±13%, MVD count 78±15.2). The 14D cuff-off group had severe atrophy (56±16.6%) and reduced MVD count (94±20.1) similar to that seen in 28D RAS group. 50% of mice that developed hypoxia at day 3 had an improvement in their oxygenation after cuff removal at day 7, whereas, mice undergoing cuff removal at day 14 and 28 day ras mice remained hypoxic.

Conclusion: Based on these results, we conclude that the renal architecture and microvessel density are preserved when the cuff is removed no longer than 7 days post surgery. We identified that 2 weeks after cuff placement is the "point of no return" in the renal injury in murine RAS model due to their reduction in microvessel density. Studies to identify biomarkers associated with irreversible renal injury in this model are currently being performed.

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