Losartan reduces ensuing CKD and mortality after AKI

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INTRODUCTION

Acute kidney injury (AKI) is responsible for approximately 2 million deaths annually worldwide. There is substantial progress in the field of AKI over the past 10 years. The previous conventional wisdom that AKI survivors with fully recovered renal function tend to do well appears to be flawed. In agreement with the other independent studies, not only the risks for cardiovascular events and long-term mortality but also the ensuing chronic kidney disease (CKD) and end-stage renal disease (ESRD) increased substantially after discharge from hospital in our cohort of dialysis-requiring AKI patients. Reduction in renal mass and nephron number appears to be an important determinant of the ensuing CKD in AKI patients; however, the molecular mechanisms underlying the AKI- CKD transition remain illusive. This study was therefore conducted to establish a murine model of AKI-CKD continuum and then delineate the mechanisms underlying the ensuing CKD progression after functional recovery from AKI.

METHODS

Adult (8-12 weeks) male CD1 mice were anesthetized with ketamine/xylazine (100/10 mg/kg, intraperitoneally) and subjected to right NX. Two weeks later, left kidney was clamped with a non-traumatic micro-aneurysm clip to perform IRI under the homeothermic blanket system (Stoelting Co. Wood Dale, IL) which contained a rectal thermal probe and a heating pad to maintain the core body temperature at 37^{oC}. Right NX only was performed in control mice. NX+IRI mice were divided into 3 groups receiving vehicle (drinking water only), losartan potassium (0.1 g/L in the drinking water; Sigma, St. Louis, MO), or hydralazine hydrochloride (0.06 g/L in the drinking water; Sigma) from one month after IRI surgery. Age- matched NX mice served as the control.

RESULTS

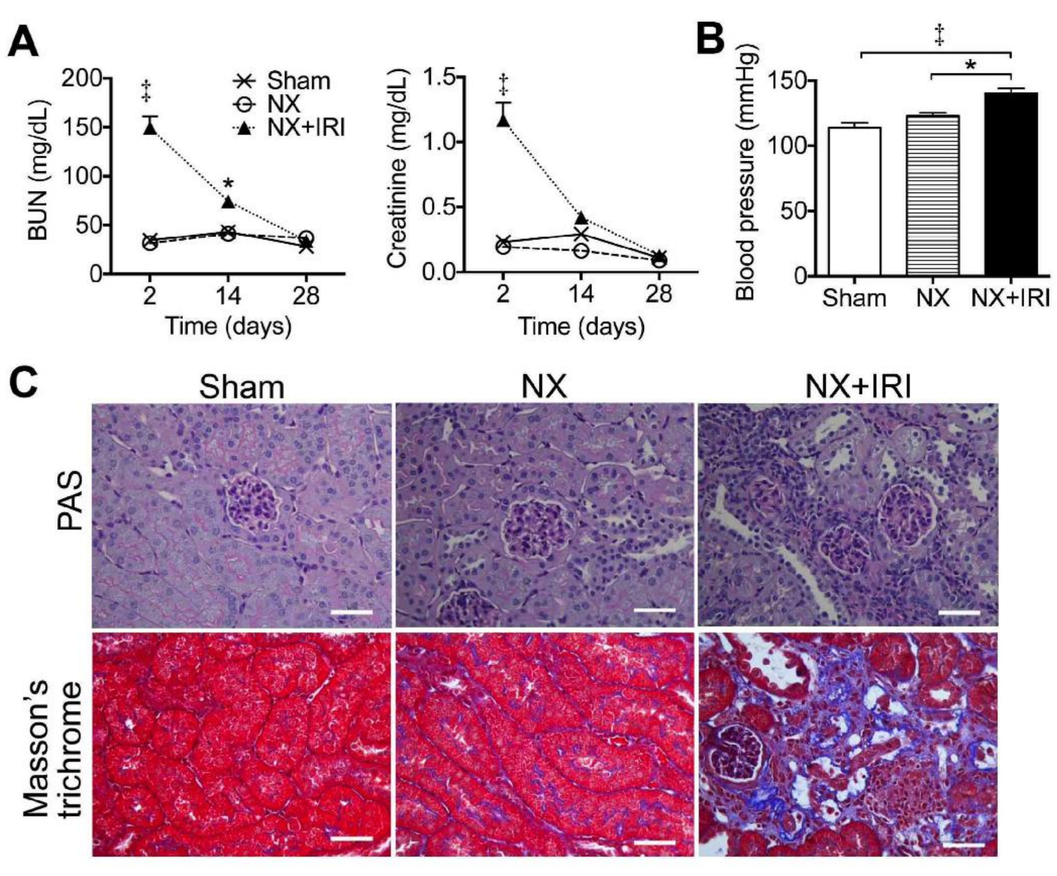

Figure 1. A murine AKI model shows abnormal renal pathology and ongoing injury after functional recovery. **(A)** Time course of blood urea nitrogen (BUN) and creatinine plasma levels in adult male mice subjected to sham operation, nephrectomy (NX) and NX followed by contralateral renal ischemia-reperfusion injury (NX+IRI). **(B)** Systolic blood pressure (BP) at day 28. **(C)** Representative images of periodic acid-Schiff (PAS) and Masson's trichrome stain of kidneys at day 28. Scale bar, 100 μm.

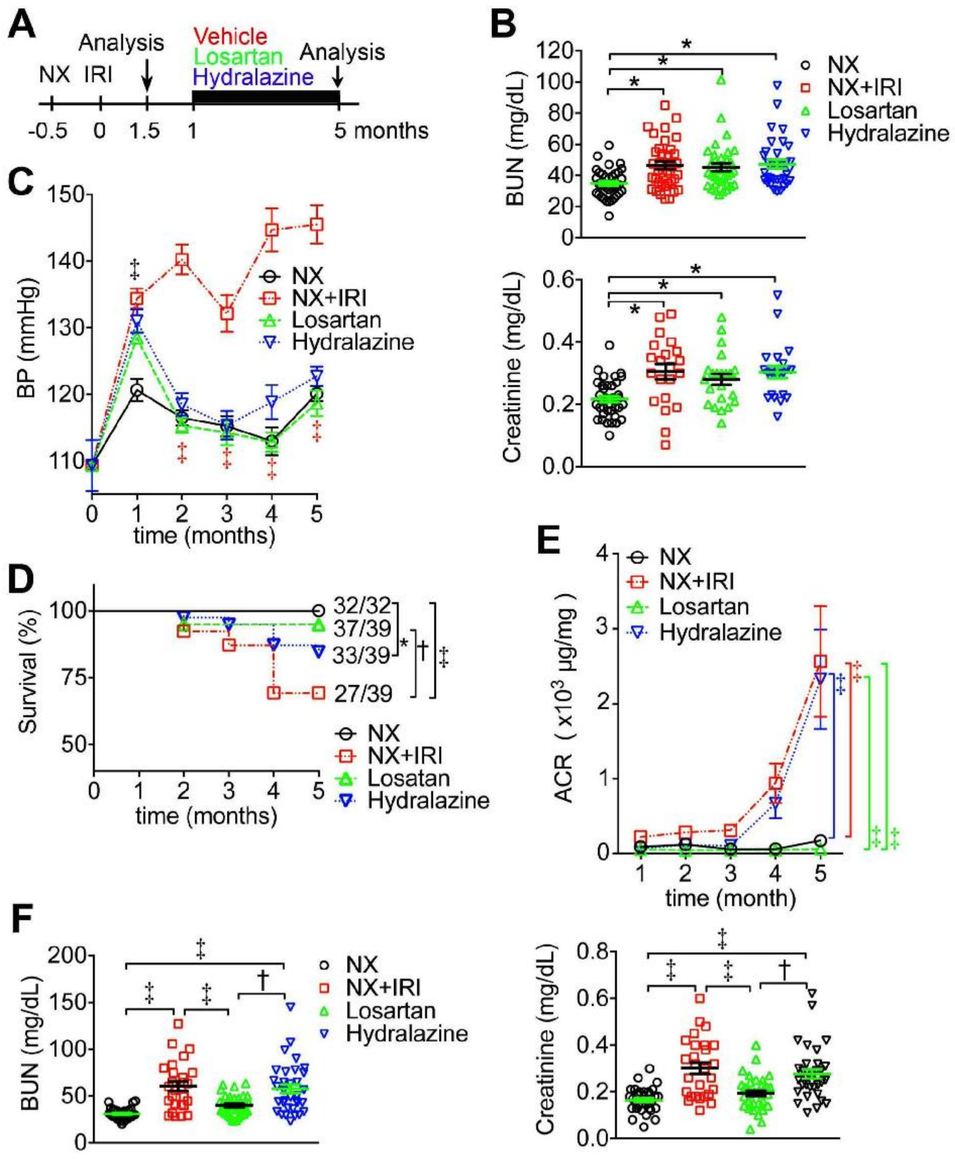

Figure 2. Losartan reduces mortality and ensuing CKD after severe AKI. **(A)** Plasma BUN and creatinine were analyzed 14 and 27 days after IRI or sham surgery and then the mice were administered water vehicle, losartan, or hydralazine since 1 month after NX+IRI. NX only mice served as the sham control. All mice were sacrificed for analyses 5 months after surgery. *N* for each group at each time point was shown in (D). **(B)** Plasma levels of BUN and creatinine 14 days after surgery. *n*=32 in NX group, and 39 for each group of NX+IRI. Each symbol represents the data from each mouse. **(C)** Time course systolic BP. NX *versus* other 3 groups at 1 month; NX+IRI *versus* other 3 groups at 2, 3, 4, and 5 month. **(D)** The percentage of survival. **(E)** Time course urine ACR. **(F)** Plasma levels of BUN and creatinine at 5 month when *n*= 32 (NX), 27 (NX+IRI), 37 (Losartan) and 33 (Hydralazine) as shown in (D). Data are expressed as mean + SEM in (B), (C), (E) and (F). **P*<0.05, †*P*<0.01, ‡*P*<0.001.

CONCLUSIONS

In conclusion, mice after 2-step surgery including NX followed by IRI of contralateral kidney represent a good model for studying AKI-CKD continuum. Our data support ongoing injury and RAS activation in the repairing kidneys after AKI. RAS blockade with losartan is effective to reduce ensuing CKD and mortality.

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