SP088

The abrogation of endothelial-expressed hypoxia-inducible factor 2 α (*HIF2α*) mediates endothelial dysfunction and glomerular lesions during hypertensive nephropathy

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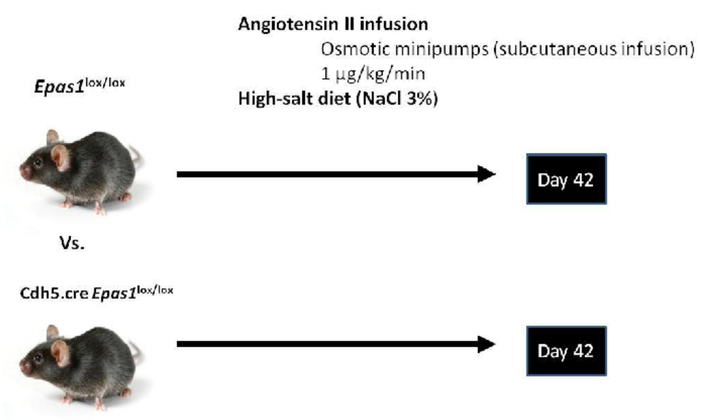
INTRODUCTION

- After diabetes, hypertension is the second leading cause of chronic kidney disease. Accumulating evidence suggests that chronic hypoxia is a final common pathway of end-stage kidney failure in chronic kidney disease[1].
- Hypoxia inducible factors (HIF) mediate tissue specific hypoxia responses and are highly expressed in the kidney[2].
- In particular, it has been demonstrated that endothelial HIF2α/Epas1 can protect mice from ischemia-reperfusion related kidney injuries[3].
- **Our study evaluates the role of endothelial HIF2α (Epas1) during angiotensin II induced hypertensive nephropathy.**

METHODS

Endothelial-specific disruption of *Epas1* alleles encoding for HIF2α was generated by crossing cdh5-Cre-positive mice[4] (expressing Cre recombinase under the control of the cadherin 5 promoter) with the *Epas1*$^{lox/lox}$ mice[5] on a C57BL6/J background.

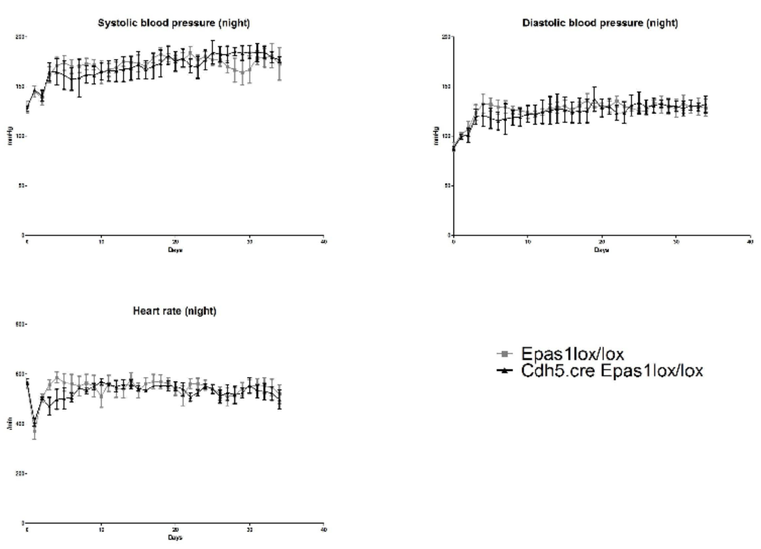
We infused angiotensin II (1µg/kg/min) to endothelial *Hif2a* knock-out mice (Cdh5.cre *Epas1* $^{lox/lox}$) and their littermates (*Epas1* $^{lox/lox}$) for 42 days. Both groups have been submitted to 3% NaCl high-salt diet.



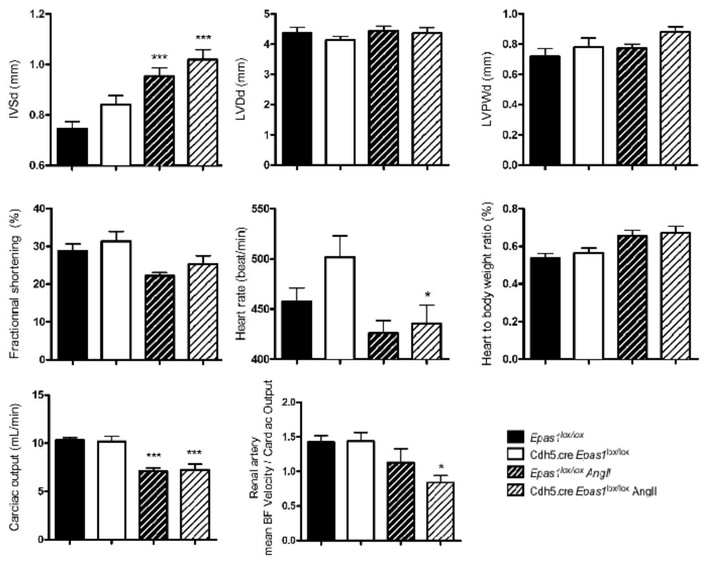
RESULTS

1.Systemic hemodynamics are not affected by endothelial HIF2α abrogation during hypertensive nephropathy

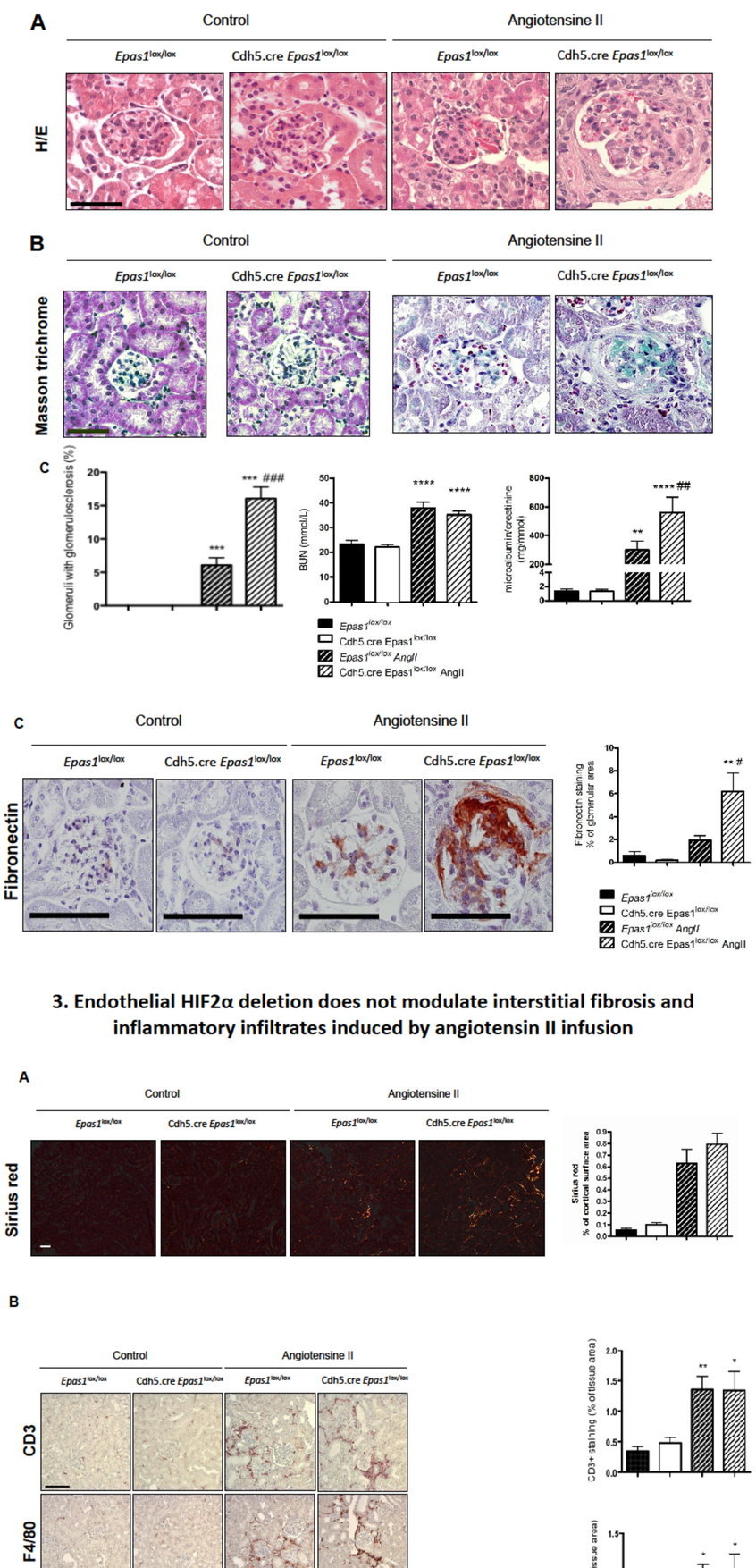
a. Direct blood pressure monitoring via implantable radio telemetry during angiotensin II infusion



b. Non-invasive ultrasound study of cardiac and renal hemodynamics before and after angiotensin II infusion

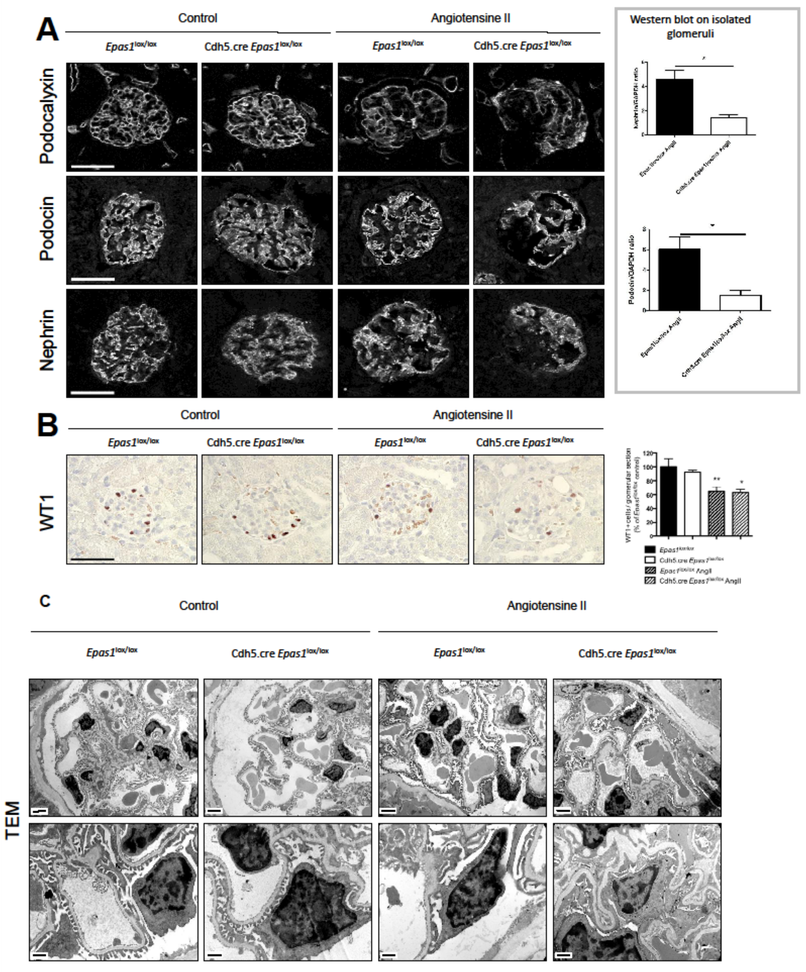


2.Endothelial Hif2α deletion leads to increased albuminuria and glomerular sclerotic lesions during hypertensive nephropathy

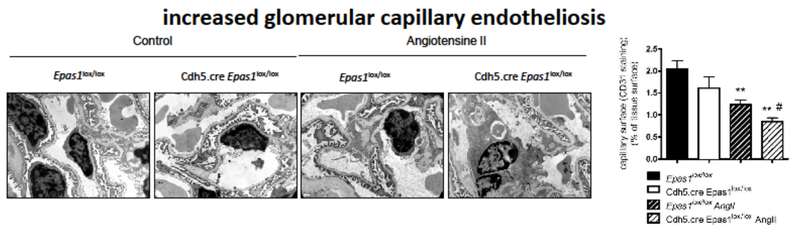


3. Endothelial HIF2α deletion does not modulate interstitial fibrosis and inflammatory infiltrates induced by angiotensin II infusion

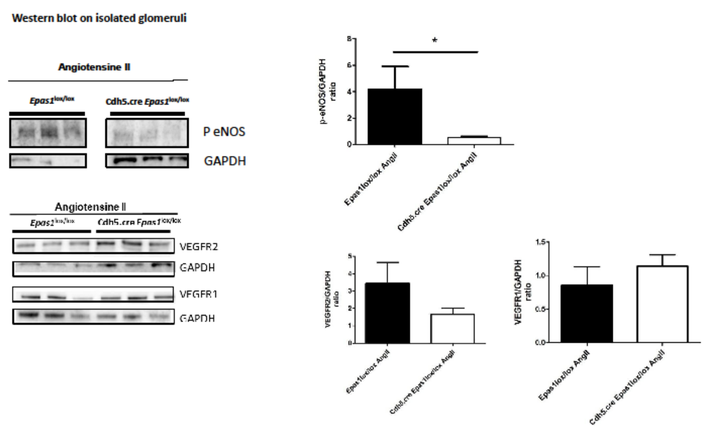
4. Endothelial Hif2α deletion aggravates podocyte injury induced by angiotensin II infusion



5. HIF2α deficient mice displayed decreased renal capillary density and increased glomerular capillary endotheliosis



6. Endothelial nitric-oxyde synthase (eNOS) phosphorylation appeared blunted in glomeruli from mice with HIF2α endothelial deficiency



CONCLUSIONS

- Although both groups presented identical blood pressures both at baseline and during chronic angiotensin II infusion, endothelial-specific *Hif2a* deletion accentuated both glomerular damage and albuminuria. HIF2α deficient mice displayed decreased renal capillary density and endothelial swelling.
- Surprisingly, endothelial-specific *Hif2a* deficiency caused severe podocytic lesions that include foot processes fusion and extracellular matrix deposition in glomeruli.
- Moreover, endothelial nitric oxide synthase phosphorylation appeared blunted in HIF2α deficient glomeruli
- **In conclusion, our study shows that endothelial HIF2α plays a protective role during glomerular hypertensive related injuries. This role appears to be independent of blood pressure levels**. As previously demonstrated in diabetic nephropathy[6], hypertension-associated podocytic lesions may have been related to impaired glomerular nitric oxide pathway response. This data suggests that endothelial HIF2α can mediate glomerular nitric oxide production and crosstalk to podocytes during hypertensive nephropathy limiting glomerulosclerosis.

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