Research Week 2022

Cardiac arrest induced systemic ischemia alters phenotype of renal ischemia reperfusion

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Keywords

Acute kidney injury, Chronic kidney disease, Cardiorenal syndrome type1, AKI-CKD transition

Abstract

Introduction: Cardiorenal syndrome type 1 (CRS1) is acute kidney injury (AKI) due to rapid worsening of cardiac function, and is a common cause of AKI. Ischemic AKI and subsequent chronic kidney disease (CKD) is mainly investigated by using the model of renal pedicle clamp (ischemia-reperfusion injury: IRI) which models renal transplant warm ischemia. However, results from IRI do not mimic clinical CRS1. We have previously identified a cardiac-derived soluble factor, cardiac LIM protein (CSRP3), which mediates renal function. We hypothesized that the phenotype of AKI-CKD transition differs between animal models of systemic ischemia and renal-limited ischemia.

Methods: Mice were subjected to 8-minute cardiac arrest and cardiopulmonary resuscitation (CA/CPR), or IRI. 24h and 49 days after surgery, glomerular filtration rate (GFR; uL/min/100g) was assessed and urine, blood, kidney and heart samples were collected.

Results: Using a time-titration protocol, we found that the GFR 24h after surgery was equivalent between 27min IRI and eight min CA/CPR ($p=0.999$). Eight-minute IRI, the same duration as CA/CPR, resulted in higher GFR than CA/CPR ($p<0.001$). 49 days after surgery, GFR of CA/CPR was equivalent to that of 8min IRI, but blood urea nitrogen and cystatin-C of CA/CPR were higher than 8min IRI, suggesting milder chronic injury from 8 min IRI. GFR of CA/CPR was higher than that from 27min IRI ($p<0.05$). Eight-minute IRI animals demonstrated albuminuria, 27min IRI showed proteinuria and albuminuria, but CA/CPR demonstrated neither albuminuria nor proteinuria. Expression of CSRP3, in the heart was elevated after CA/CPR but not after IRI.

Conclusion: Cardiorenal AKI (CA/CPR) and local ischemia (IRI)-induced AKI demonstrated different phenotypes in AKI-CKD transition, with principal differences being degree of chronic filtration loss and development of albuminuria. Extra-renal soluble factors, such as CSRP3, may mediate transition.