

Catheter-based renal sympathetic denervation induces reversible acute kidney injury and myocardial damage through the activation of caspase-1 and NLRP3 inflammasome

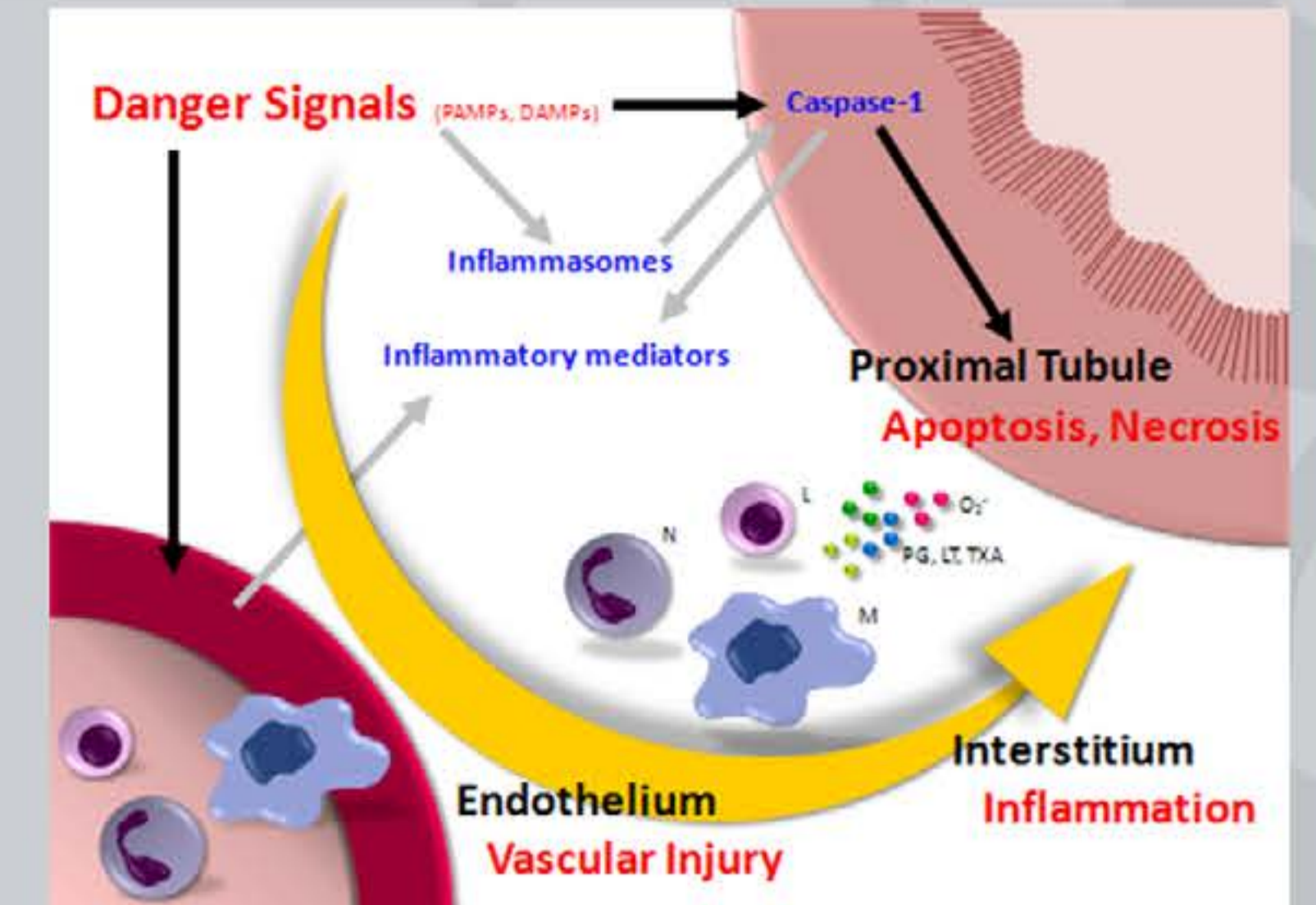
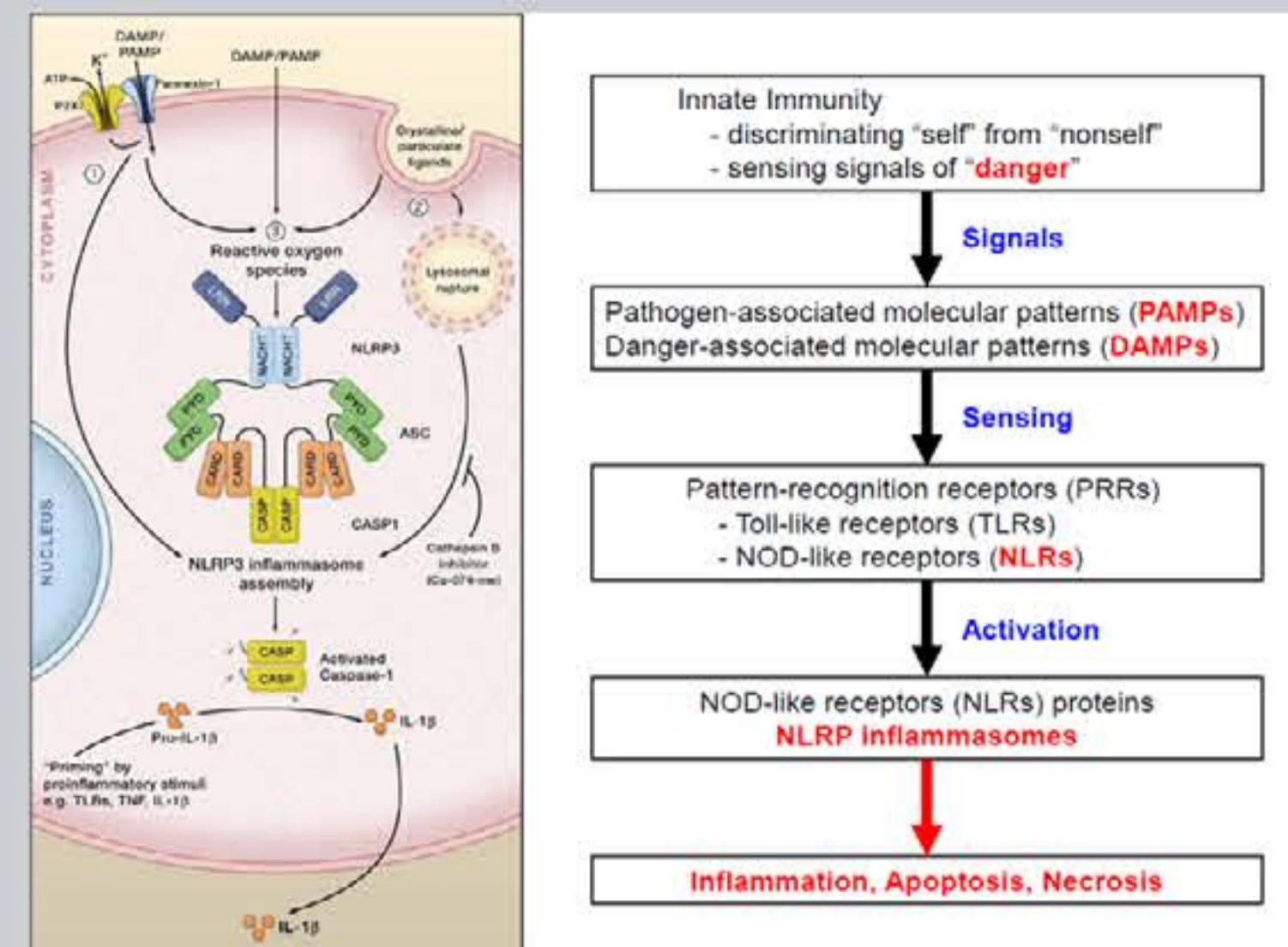
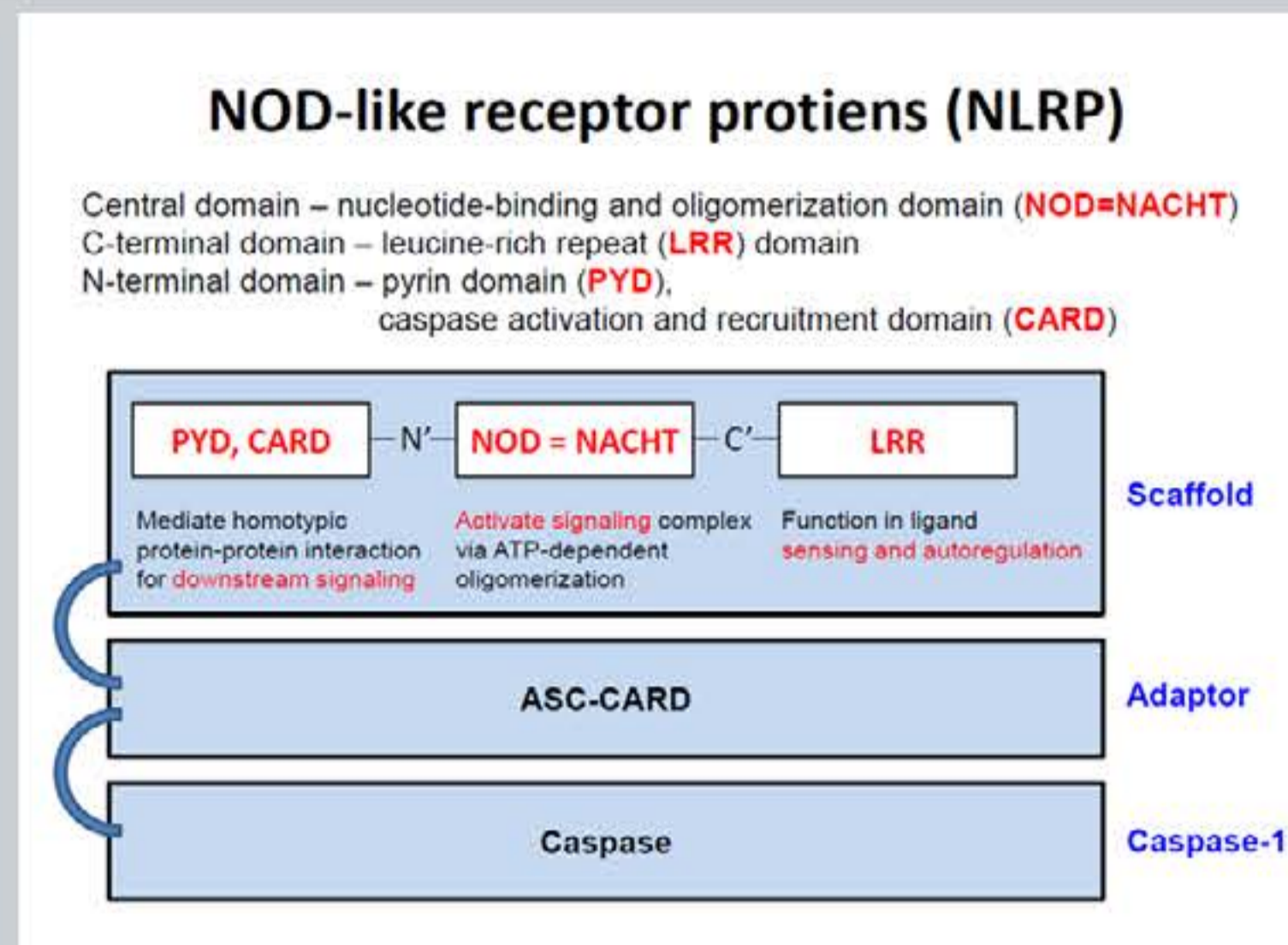
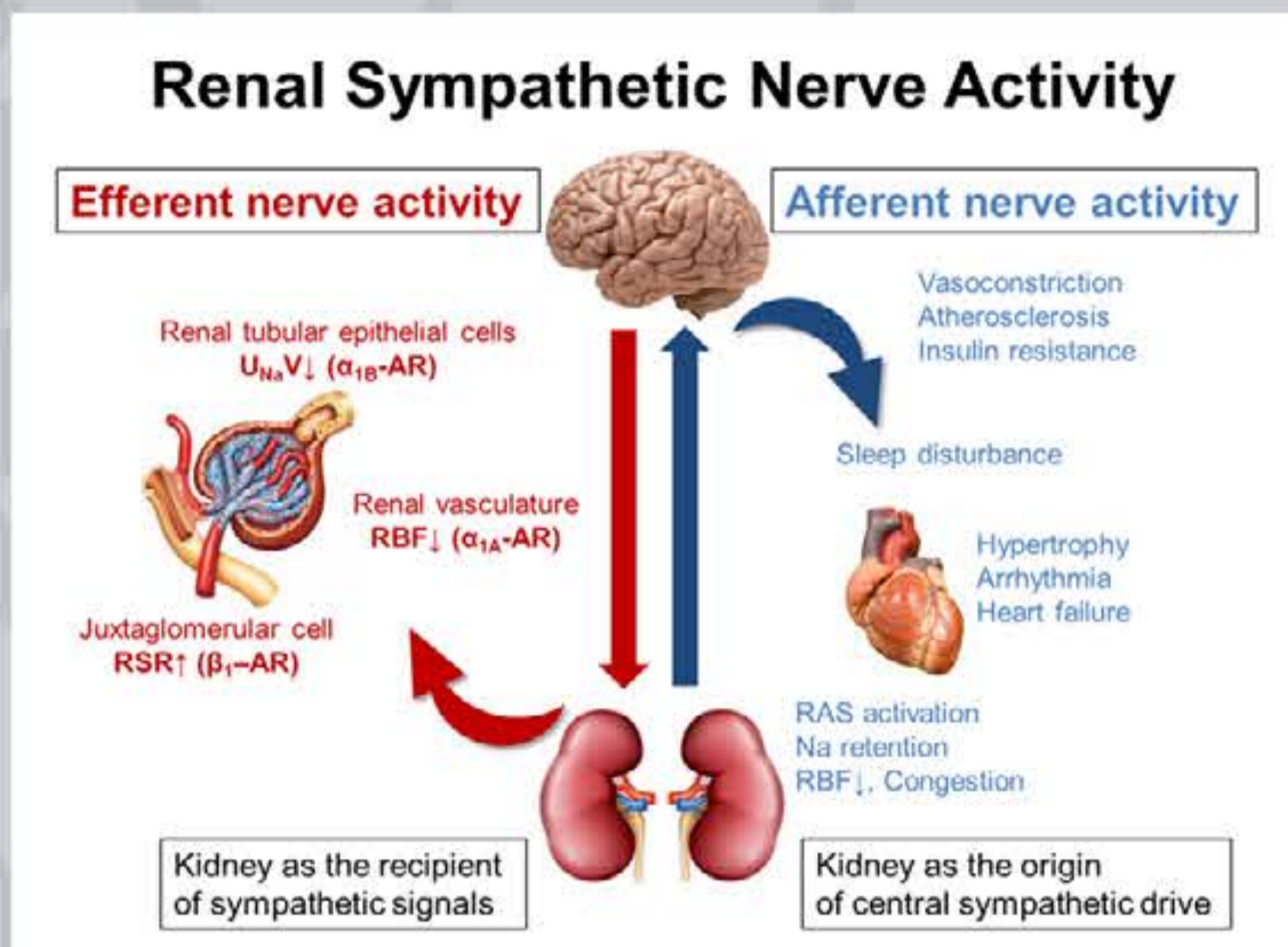
Dong Won Lee*, Jeong-Su Kim, Il Young Kim, Joo Hui Kim, Harin Rhee, Eun Young Seong, Sang Heon Song, Soo Bong Lee, and Ihm Soo Kwak

Department of Internal Medicine, Pusan National University School of Medicine, Yangsan, Busan, Korea

INTRODUCTION & OBJECTIVES

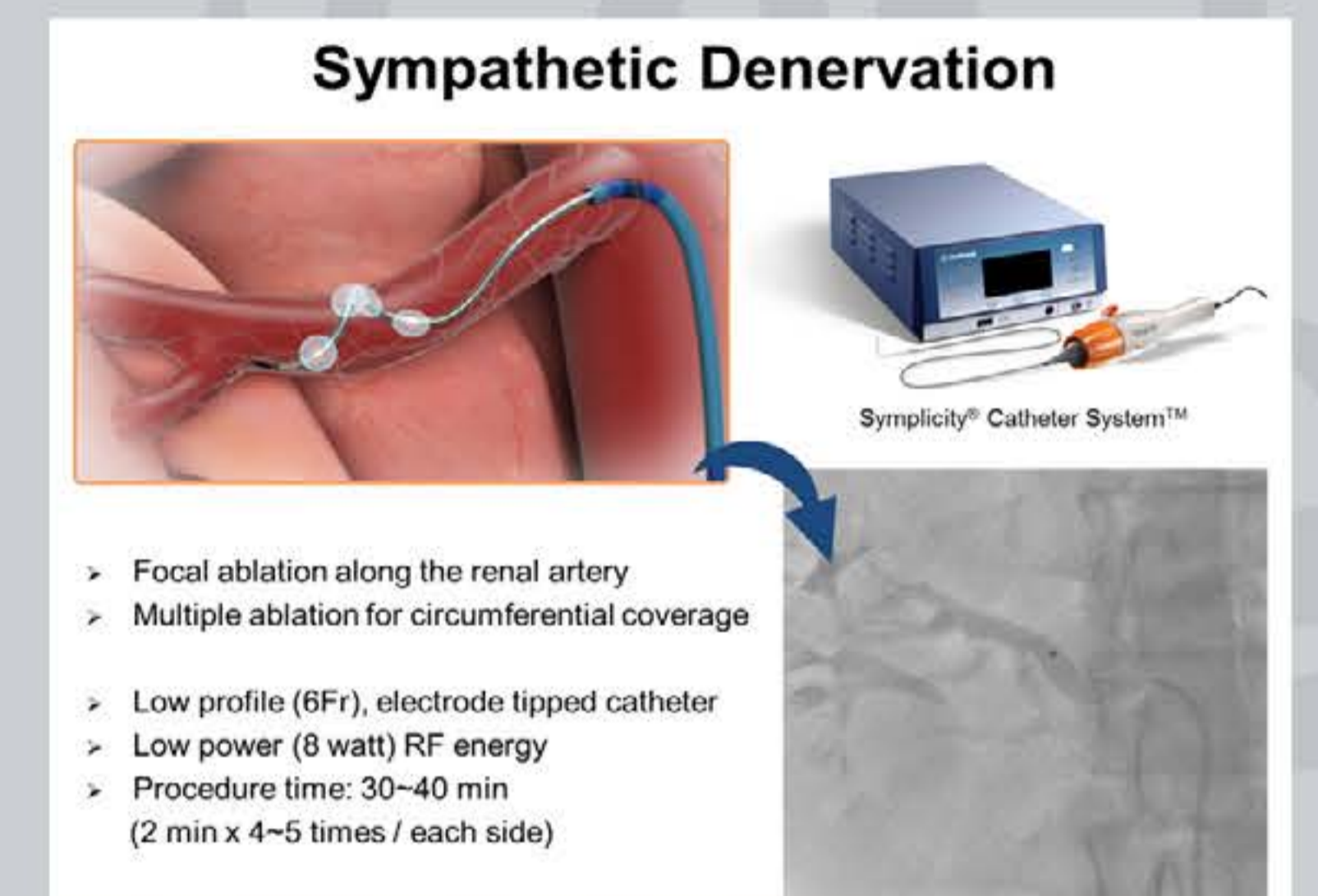
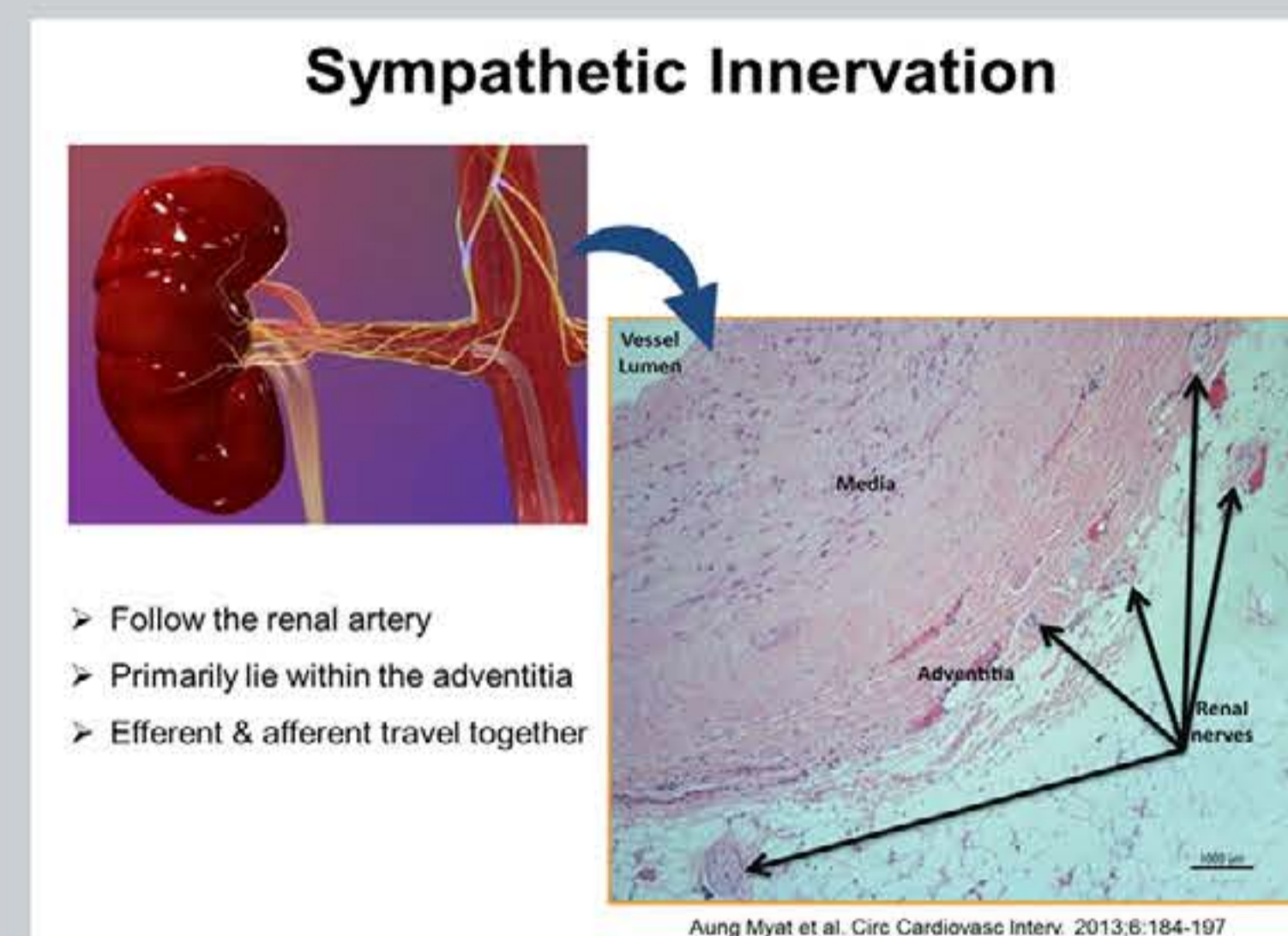
Catheter-based renal sympathetic denervation (RDN) is available and implemented as a strategy for the treatment of resistant hypertension and is currently under clinical investigation. In the aspect of chronic safety, renal function, as assessed by serum creatinine, eGFR (MDRD), and cystatin C was reported to be unchanged from baseline at 6 months.

We investigated whether RDN might cause subtle inflammation and subclinical damage in the early phase of acute kidney injury (AKI).



METHODS

Female pigs were divided into 5 groups; normal control (group A), Sham-operated control (group B), and RDN groups subdivided into 3 groups according to the time of sacrifice; immediately (group C), 1 week later (group D), and 2 weeks later (group E) after RDN. We checked IL-1α, 1β, 18, 6, 10, TNF-α, cystatin C, caspase-1, ASC, and NLRP3 in renal cortex as early biomarkers of inflammation & AKI.



RESULTS

- There were no significant changes between group A and B. Serum creatinine and cystatin C were increased from the 1st to the 2nd week after RDN with no statistical significance. **Serum LDH** was increased immediately after RDN until the 1st week, and then decreased at the 2nd week.
- In the kidneys**, pro-inflammatory cytokines, **IL-1β, -18, -6, TNF-α**, and anti-inflammatory cytokine **IL-10** were increased immediately, and then decreased at the second week after RDN. **IL-1α** was increased at the first week, and decreased at the second week after RDN. **Caspase-1** was increased immediately after RDN until the second week. **ASC** and **NLRP3** expressions were increased immediately, and then decreased at the second week after RDN.
- In the myocardium**, **IL-1β, -10, TNF-α** and **ASC** were increased at the first week or immediately, and then decreased at the second week after RDN. **Caspase-1** was increased immediately until the second week after RDN. However, NLRP3 expression in the myocardium did not show any significant differences between groups.

Table 1. Chemical parameters in AKI after RDN

	Normal	Sham	RDN-0	RDN-1	RDN-2
Hb (g/dL)	10.3±0.5	9.7±0.2	9.6±0.3	11.4±1.4	10.5±1.1
BUN (mg/dL)	6.4±0.4	7.1±1.7	9.0±0.5	6.6±0.7	8.9±1.1
SCr (mg/dL)	0.9±0.1	0.9±0.0	1.1±0.0	1.3±0.0	1.2±0.0
LDH (U/L)	745.3±24.1	796.3±46.1	1159.7±132.3*	1131.0±166.7*	836.0±18.9**
Na (mEq/L)	142.3±1.5	140.3±0.9	142.0±0.0	143.3±0.9	142.3±0.3
K (mEq/L)	4.0±0.2	3.8±0.2	4.3±0.1	4.5±0.3	4.5±0.4
Cl (mEq/L)	102.7±0.9	101.3±0.9	103.0±0.6	100.3±1.3	98.0±1.5
CRP (mg/L)	0.09±0.04	0.02±0.00	0.09±0.01	0.02±0.00	0.03±0.01
Cysc (mg/L)	0.00±0.00	0.00±0.00	0.17±0.09	0.27±0.03	0.27±0.03
UPCR (mg/g)	154.5±16.7	153.8±1.5	188.8±9.7	150.4±22.8	118.9±17.3
UACR (mg/g)	7.5±3.3	3.5±1.2	3.1±1.1	4.0±1.8	2.4±0.3

Figure 2. Pro-/Anti-inflammatory cytokines in AKI after RDN

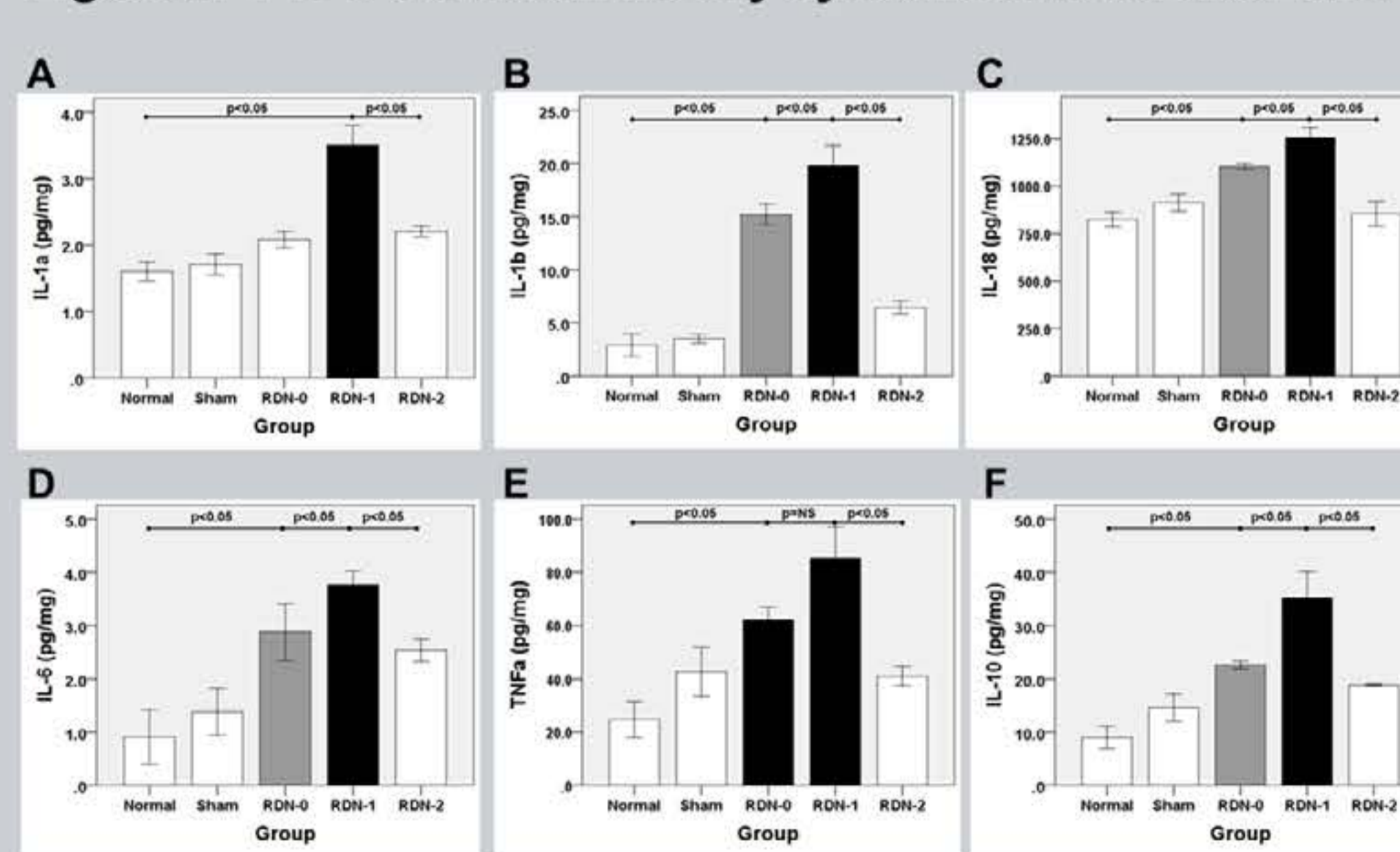


Figure 4. Pro-/Anti-inflammatory cytokines in myocardial Damage after RDN

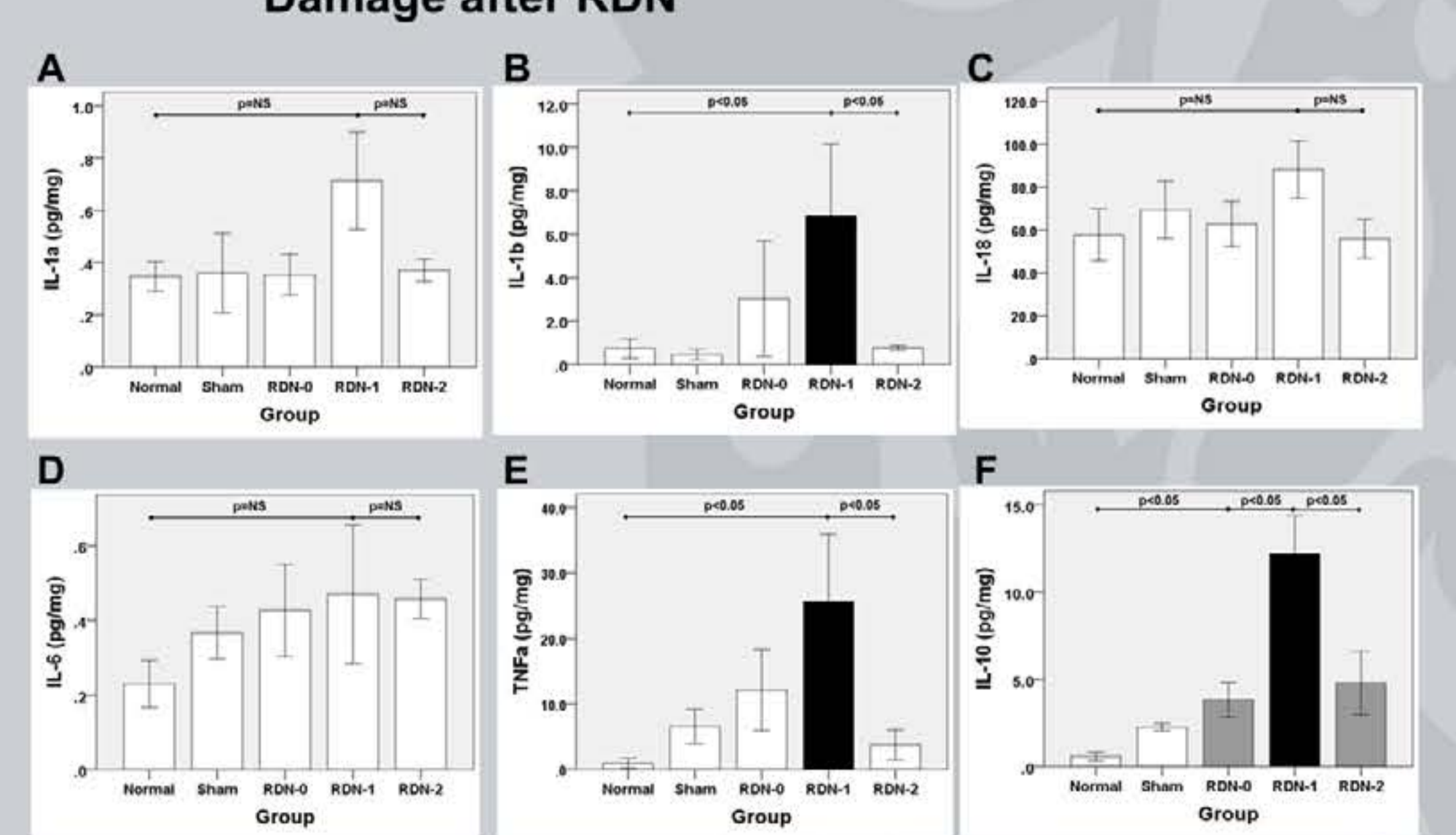


Figure 1. Induction of reversible AKI after RDN

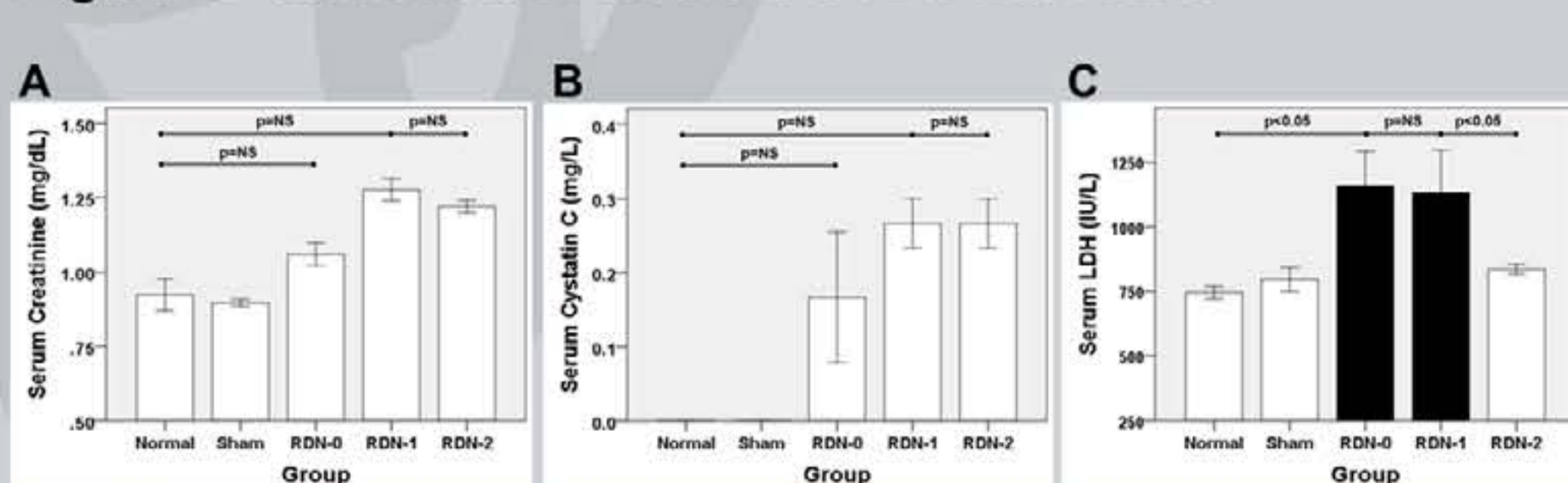


Figure 3. Renal ASC, NLRP3 and caspase-1 in AKI after RDN

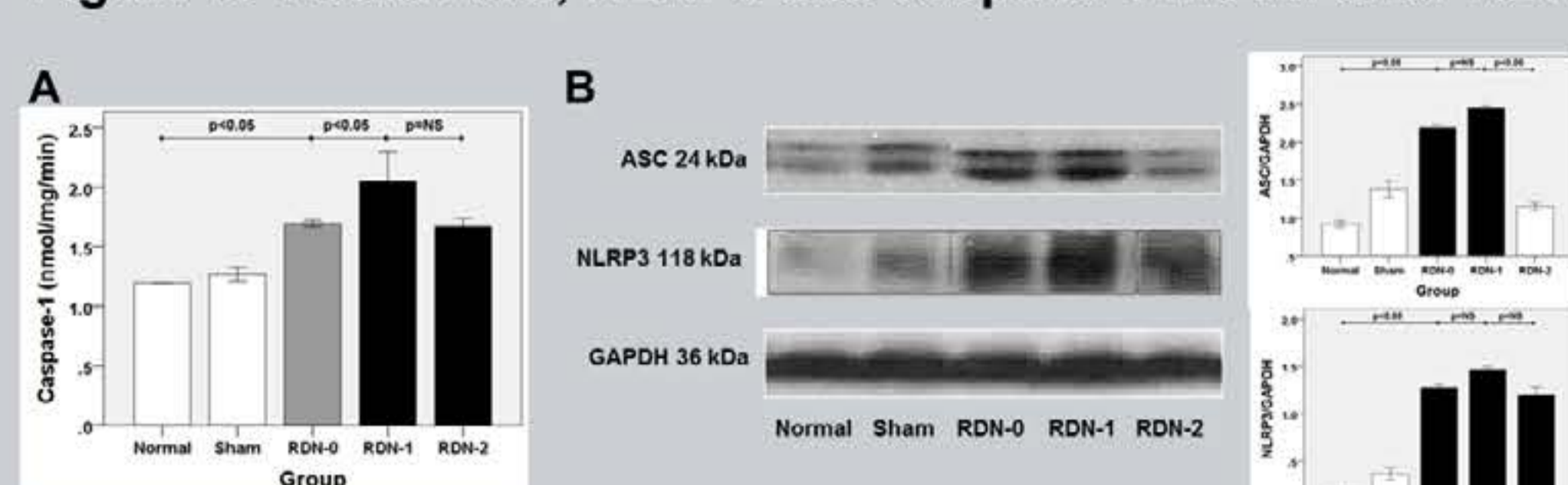
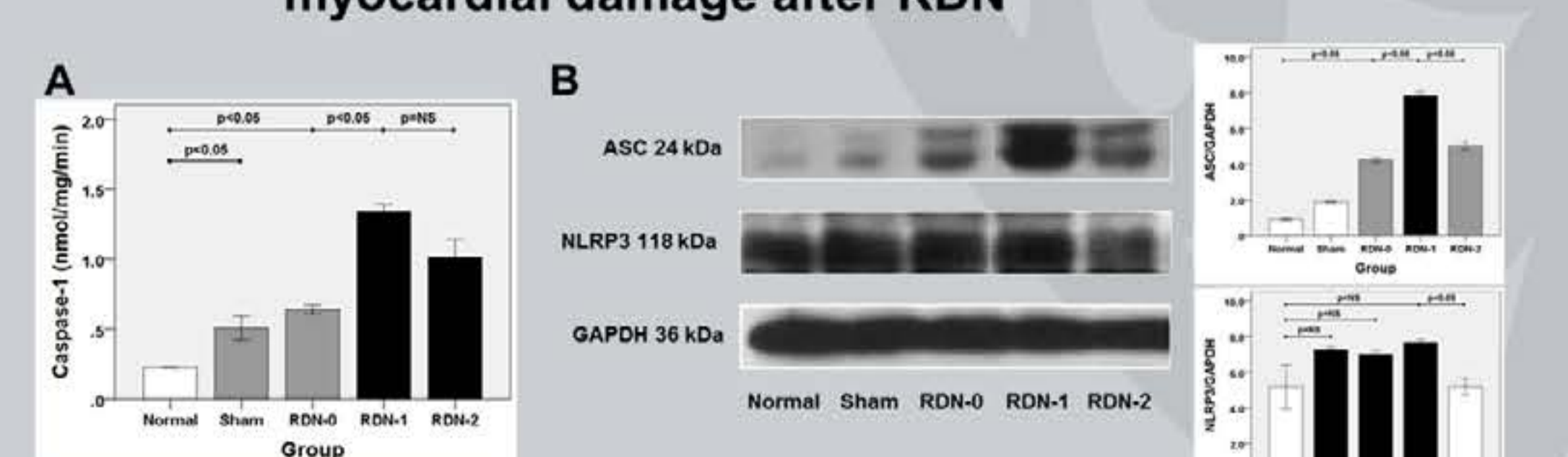


Figure 5. Myocardial ASC, NLRP3 and caspase-1 in myocardial damage after RDN



CONCLUSION

RDN procedure is safe, however, **can cause transient AKI and myocardial damage** through the **activation of pro-inflammatory cytokines, caspase-1 and NLRP3 inflammasome**.