The cardiac dysfunction caused by sepsis in animals with chronic kidney disease is attenuated by inhibiting I kappa B kinase

P144

THE CARDIAC DYSFUNCTION CAUSED BY SEPSIS IN ANIMALS WITH CHRONIC KIDNEY DISEASE IS ATTENUATED BY INHIBITING I.B KINASE

J. Chen1, J. Kieswich1, F. Chiazza2, T. Gobbetti1, N.S. Patel1, M. Perretti1, M. Collino2, M.M. Yaqoob1, and C. Thiemermann*1.

1Queen Mary University of London, William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, London, United Kingdom,
2University of Turin, Department of Drug Science and Technology, Turin, Italy

Patients with chronic kidney disease (CKD) requiring dialysis have a higher risk of sepsis and a 100-fold higher mortality than the general population with sepsis. The severity of cardiac dysfunction is an important predictor of mortality among patients with sepsis. Having discovered that pre-existing CKD worsens the cardiac outcome in mice with sepsis (1), we have investigated whether inhibition of I.B kinase (IKK) reduces the cardiac dysfunction in these animals.

Male C57BL/6 mice were subjected to a two-stage, 5/6th nephrectomy (SNX). After 8 weeks, mice with SNX/CKD were subjected to either low dose LPS (2mg/kg) or cecum ligation and puncture (CLP) (fluid and antibiotics given at 6h and 18h after CLP). At 18h after LPS injection or 24h after CLP, cardiac function was evaluated by echocardiography. When compared to sham mice, SNX for 8 weeks resulted in a significant rise in urea and creatinine and a small (PG0.05) reduction in ejection fraction (EF). In sham mice without CKD, low dose LPS or CLP had no effect on EF, lung myeloperoxidase (MPO) activity orsystemic cytokine levels. In CKD mice, LPS or CLP caused profound cardiac dysfunction (Fig. 1A), increased lung MPO activity and increased plasma cytokine levels (TNF-!, IL-1", IL-6, IL-10). Compared with sham mice, cardiac biopsies obtained from CKD mice showed increases in the phosphorylation of IkBa, nuclear translocation of the NF-kB subunit p65, increased iNOS expression, and significant increases in phosphorylation of Akt and ERK1/2. Moreover in CKD mice, LPS or CLP further increased the phosphorylation of IkBa, the nuclear translocation of p65 and the iNOS expression. Treatment of CKD mice with the IKK inhibitor IKK 16 (1 mg/kg, 1 h after CLP) attenuated cardiac dysfunction (Fig. 1B), increase in lungMPO activityand cytokine formation caused by CLP. IKK 16 also reduced the i) increased phosphorylation of I.B!; ii) increased nuclear translocation
of p65; and iii) significant increase in iNOS expression in CKD hearts subject to CLP.

In conclusion, the presence of CKD aggravates the cardiac dysfunction caused by LPS or CLP in the mouse; and this may (at least in part) be due to increased cardiac activation of NF-.B and increased iNOS expression.

(1) Chen et al, Shock 2014;41(Supplement 2):40

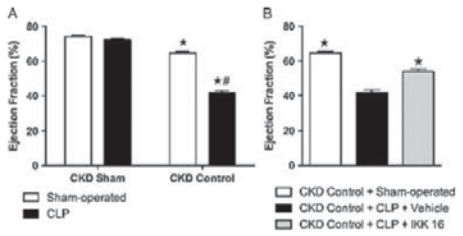

FIG. 1 **Effects of pre-existing CKD and IKK 16 treatment on EF in mice that undertwent CLP.** (A) *P<0.05 versus CKD sham group with respective treatment, #P <0.05 versus respective sham-operated group; (B) *P<0.05 versus CKD Control +CLP−Vehicle group.