Erythropoietin Attenuates Cardiac Dysfunction Caused by Endotoxaemia in Mice

Areeg Khan¹, Sina Coldewey¹,², Yasunori Shintani¹, Ken Suzuki¹, Nimesh Patel¹, Christoph Thiemermann¹

¹William Harvey Research Institute, Translational Medicine and Therapeutics, EC1M 6BQ, United Kingdom, ²Hannover Medical School, Department of Anaesthesiology and Intensive Care Medicine, 30625, Germany

Background Sepsis is the leading cause of mortality and morbidity in the critically ill, largely as a consequence of multiple organ failure (MOF). Erythropoietin (EPO), a pleitropic cytokine has been shown to ameliorate organ dysfunction/injury in mouse models of ischaemia/reperfusion, as well as sepsis. Here we investigate the role of recombinant human EPO in a mouse model of endotoxin-induced cardiac dysfunction.

Methods Sixty C57/BL6 mice (Harlan Laboratories, UK; 25-30 g) were administered LPS (9 mg/kg i.p., 5 ml/kg). Mice were treated with EPO (1000 IU/kg s.c., 5 ml/kg) 1 h after the administration of LPS. Eighteen hours after the administration of LPS markers of organ dysfunction/injury were measured: serum urea and creatinine as markers of renal dysfunction, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) as markers of liver injury, and lung myeloperoxidase (MPO) activity as a marker for polymorphonuclear leukocyte (PMN) infiltration. Cardiac function was assessed by echocardiography by measuring the following parameters - ejection fraction (EF), fractional shortening (FS), and fractional area of change (FAC). Data were analysed using one-way ANOVA, followed by a Dunnett’s post hoc test. A P-value of less than 0.05 was considered significant.

Results When compared to sham-operated mice the administration of LPS caused significant increases in serum urea (6±0.33 to 28±1.22 mmol/L, P<0.05), and creatinine (31±0.97 to 45±3.01 μmol/L, P<0.05, Figure 1A), serum ALT (39±2.28 to 59±6.24 U/L, P<0.05) and AST (66±3.19 to 165±18.45 U/L, P<0.05), lung MPO activity (45±11.50 to 130±7.72 μU/g, P<0.05, Figure 1B), and significantly reduced EF (80±1.75 to 31±3.74 %, P<0.05, Figure 1C), FS (48±1.76 to 14±1.90 %, P<0.05) and FAC (60±1.83 to 21±2.12 %, P<0.05), which suggests MOF. Administration of EPO 1 h after LPS significantly attenuated the endotoxaemia-induced increases in serum urea (28±1.22 to 23±0.96 mmol/L, P<0.05) and creatinine (45±3.01 to 37±1.62 mmol/L, P<0.05, Figure 1A), and the increases in lung MPO activity (130±7.72 to 72±9.56 μU/g, P<0.05, Figure 1B). However, the administration of EPO 1 h after LPS did not attenuate the endotoxaemia-induced increases in serum ALT and AST. More importantly EPO treatment significantly attenuated the endotoxaemia-induced elevation in EF (31±3.74 to 49±2.61 %, P<0.05, Figure 1C), ES (48±1.76 to 24±1.58 %, P<0.05) and FAC (21±2.12 to 34±3.49 %, P<0.05).

Conclusion These data demonstrate that administration of LPS causes significant renal dysfunction, liver injury, lung inflammation and cardiac dysfunction at 18 h. The administration of EPO to endotoxaemic mice attenuates the renal dysfunction, lung inflammation and, for the first time, cardiac dysfunction 18 h after the administration of LPS. The mechanism by which EPO affords cardiac protection is unknown and warrants further investigation.
Figure 1: Effect of erythropoietin (EPO) on (A) renal dysfunction assessed by the alteration in serum levels of creatinine (all groups, n=11), (B) lung inflammation assessed by the alteration in myeloperoxidase (MPO) activity (all groups, n=4), and (C) cardiac dysfunction assessed by determining the percentage ejection fraction (EF) (all groups, n=6), in mice treated with saline (Sham-Control, 5ml/kg i.p.), LPS (LPS-Control, 9mg/kg i.p.), or EPO (LPS-EPO, 1000U/kg s.c.) 1 h after LPS. Data represent mean ± SEM for n number of observations, *P < 0.05 vs. LPS-Control group.

AK is supported by a MRC PhD Studentship, SC is supported by a Deutsche Forschungsgemeinschaft Fellowship, YS is supported by a MRC New Investigator Award, NP is funded by a Kidney Research UK Fellowship (PDF4/2009), and this work was in part funded by the William Harvey Research Foundation.