Toll-like receptor 4 dependent inflammation in low tidal volume mechanical ventilation

Mechanical ventilation may induce lung injury but the underlying mechanisms are largely unknown. Vaneker et al. tested the hypothesis that endogenous ligands, the so-called danger signals, may induce ventilator-induced lung injury (VILI) through a Toll-like receptor 4 dependent mechanism.

The authors used their previously validated mechanotransduction model in the mouse. The presence of endogenous ligands was determined by obtaining BAL fluid immediately after induction of anesthesia or after four hours of mechanical ventilation. HEK293-TLR4 cells were incubated in BAL fluid and IL-8 was measured in the supernatant. Wild type, TLR4 KO and TLR2 KO mice were ventilated with a tidal volume of 8 ml/kg and PEEP 4 cm H\(_2\)O for 4 hours. TLR-2 and TLR-4 mRNA expression, TNF-\(\alpha\), IL-1\(\alpha\), IL-1\(\beta\), IL-6, IL-10 and KC were determined in lung homogenates and plasma. Leucocyte infiltration was counted manually after Leder staining.

Mechanical ventilation induced a five-fold higher increase in supernatant IL-8 after incubation with HEK293-TLR4 cells. Co-incubation with a specific TLR-4 antagonist significantly reduced the IL-8 response. Mechanical ventilation increased the lung tissue expression of TLR4 and TLR2 mRNA. Levels of IL-1\(\beta\) and KC in lung homogenates were significantly lower in ventilated TLR4 KO mice, as were the plasma levels IL-6 and TNF-\(\alpha\). Mechanical ventilation of TLR2 KO mice did not result in significantly different cytokine levels in lung tissue and plasma compared with wild type mice. Leucocyte infiltration was less in the ventilated TLR4 KO mice.

The authors clearly show that ventilation-induced pulmonary cytokine production is partly explained by a TLR4 receptor dependent mechanism. Although the results are very interesting, it is highly unlikely that this observation will result in a major therapeutic breakthrough. TLR4 inhibition is currently being investigated in patients with severe sepsis but as many “normal” defence mechanisms also signal through the TLR4 receptor, this strategy is unlikely to be effective. This study should therefore be regarded as a step in the unraveling of this important problem.


Acute kidney injury during lung-injurious mechanical ventilation

Mechanical ventilation is associated with the development of acute kidney injury (AKI). Pulmonary cytokine production, especially IL-6 may play an important role. However how IL-6 induces AKI, is unknown. The authors tested the hypothesis that IL-6-induced increased renal endothelin 1 (ET-1) production leading to a significant decrease in renal blood flow may result in kidney dysfunction.

The experiments were performed in 27 male Wistar rats. The animals were extensively instrumented including thermodilution cardiac output measurements. Animals were divided into three groups: 1) non-ventilated, sham operated, 2) lung protective ventilation (tidal volume 6 – 8 ml/kg, PEEP 5 cm H\(_2\)O) and, 3) injurious ventilation (tidal volume 15 – 18 ml/kg, PEEP 2 cm H\(_2\)O). Animals were ventilated for four hours. During the experiment CO, creatinine clearance, fractional sodium excretion and renal blood flow were determined. After termination of the experiment, animals were killed and lung and renal histology examined. Plasma IL-6 levels and renal ET-1 levels were determined using appropriate assays.

There were only small differences in haemodynamics and gas exchange between the two ventilated groups. Renal blood flow was significantly lower in the injurious ventilation group compared with both the non-ventilated and protective ventilation groups. No differences in urine output, creatinine clearance and fractional sodium excretion were found between groups. No histopathological kidney damage was observed in any of the groups. Plasma IL-6 levels tended to increase in all three groups without significant differences. Renal ET-1 was five-fold increased in the injurious ventilation group compared with both other groups.

These results show that injurious ventilation results in an increase in renal ET-1 with a decrease in renal blood flow. These results were independent of IL-6 production and did not result in a decrease in renal function. It is likely, the time frame of four hours was too short for renal function to decline. The result of this study cannot be directly extrapolated to patient care. However, the authors offer a potential new mechanism to explain acute kidney injury in the course of mechanical ventilation.