A725 - The circadian clock protein BMAL1 regulates the severity of ventilator-induced lung injury in mice

M Felten 1 ; LG Teixeira-Alves 1 ; E Letsiou 1 ; HC Müller-Redetzky 1 ; N Suttrop 1 ; A Kramer 2 ; B Maier 2 ; M Witzenrath 1

1University Medicine Charité, Department of Infectious Diseases and Respiratory Medicine, Berlin, Germany,
2University Medicine Charité, Department of Chronobiology, Institute for Medical Immunology, Berlin, Germany

Introduction:
Mechanical ventilation (MV) is a life-saving intervention for critically ill patients, but may also exacerbate pre-existing lung injury, a process termed ventilator-induced lung injury (VILI). Interestingly, we discovered that the severity of VILI is modulated by the circadian rhythm (CR). In this study, we are exploring the role of the myeloid BMAL1, a core clock component, in VILI.

Methods:
We employed mice lacking Bmal1 in myeloid cells (LyzMCre-Bmal1-/-) and LyzMCre mice as controls. At circadian time (CT) 0 or CT12, mice were subjected to high tidal volume MV to induce VILI. Lung compliance, pulmonary permeability, neutrophil recruitment, and markers of pulmonary inflammation were analyzed to quantify VILI. To assess neutrophil inflammatory responses in vitro, myeloid cells from bone marrow of WT and Bmal1-deficient animals were isolated at dawn ZT0 (Zeitgeber time 0) and dusk (ZT12), incubated with DCFH-DA and stimulated for 15 min with PMA or PBS. Neutrophil activation (Ly6G/CD11b expression) and ROS production (DCFH-DA/Ly6G+ cells) were quantified.

Results:
Injurious ventilation of control mice at CT0 led to a significant worsening of oxygenation, decrease of pulmonary compliance, and increased mortality compared to CT12. LyzMCre-Bmal1-/- mice did not exhibit any significant differences when subjected to MV at CT0 or CT12. Mortality in LyzMCre-Bmal1-/- mice after VILI was significantly reduced compared to LyzMCre controls (CT0). Neutrophils isolated from control mice at ZT0 showed a significantly higher level of activation and increased ROS production after PMA-stimulation compared to ZT12. ROS production of LyzMCre-Bmal1-/- neutrophils did not differ from ZT0 to ZT12.

Conclusion:
The lack of the clock gene Bmal1 in myeloid cells leads to increased survival after injurious ventilation and to loss of circadian variations in neutrophil ROS production. This suggests that the internal clock in myeloid cells is an important modulator of VILI severity.