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Aspects of inflammation in acute lung injury

Experimental and clinical explorations

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Academic dissertation

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Aspects of inflammation in acute lung injury: Experimental and clinical explorations

Abstract**Background**

Acute respiratory distress syndrome (ARDS) represents a syndrome of acutely failing lung function that, by definition, requires intensive care efforts to maintain adequate oxygenation of the patient's blood. In established ARDS, treatment options are severely limited, although previous work in rodents have shown positive effects of pharmacological treatment with soluble epoxide hydrolase inhibitors (sEH) in an experimental model of acute lung injury. Clinically, the most important treatment for ARDS is reduction of harm or complications, primarily in the form of ventilator-induced lung injury (VILI). Mechanical ventilation has positive and negative effects, where avoidance of VILI induction may necessitate ventilatory settings that lead to significant patient discomfort. We do not currently have biomarkers that identify patients with inappropriate or suboptimal positive pressure ventilatory support settings.

Aims

This thesis mainly aims to describe lung injury biomarker patterns and effects of pharmacological treatment with soluble epoxide hydrolase inhibitors (sEH) in acute lung injury.

Methods

A pig model of VILI was used to identify biomarkers among oxylipins and extracellular vesicles (EVs) in plasma and in bronchoalveolar lavage fluid (BALF), and also in exhaled breath condensate (EBC). Plasma samples from a cohort of intensive care unit (ICU) subjects were used to describe the kinetics of oxylipins after intubation and in sepsis compared to non-septic cases. We also established a pig model of long-term venous access to allow for determination of pharmacokinetic properties of a potential new anti-inflammatory medication in the form of an inhibitor of sEH. Finally, sEH inhibition was tested in a lipopolysaccharide (LPS) model of lung injury in pigs.

Results

Several oxylipins increased in BALF in response to VILI induction. Some of these were also noted to increase in plasma. As a preliminary finding, a number of oxylipins could also be detected in EBC. Regarding EVs, those containing nucleic acids increased over time in response to VILI in BALF but not in plasma. In humans, lower levels of some oxylipins were observed after one day of mechanical ventilation and in septic patients compared to non-septic controls. Long-term cannulation of pigs was performed with satisfactory vascular access. Inhibition of sEH did not attenuate lung injury development after LPS challenge in pigs.

Conclusions

Some oxylipins and EVs may be markers of experimental lung injury, most clearly seen in BALF. In ICU patients, oxylipins in plasma seem to decrease after intubation and were lower among sepsis cases compared to non-septic cases in this cohort. Finally, sEH inhibition does not appear to attenuate lung injury in pigs.

Keywords: Acute respiratory distress syndrome, Ventilator-induced lung injury, Inflammation, Soluble epoxide hydrolase inhibitor, Biomarkers

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