A murine model of brain death: 
An opportunity for future mechanistic studies on treatment for donor lung injury

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Introduction: Only 15-25% of brain death (BD) donors match the ideal donor criteria for lung transplantation. The mechanisms of BD-related lung injury are not fully understood justifying further research. A successful BD model in mice would help to further investigate mechanisms to attenuate lung injury at immunological level using knock-out animals.

Materials and methods: Mice were anesthetized, tracheotomized and mechanically ventilated. Body temperature was kept constant at 36.5°C using a heating pad with temperature probe. BD was induced by gradual inflation of a subdural balloon catheter. Animals were randomly divided into 4 groups (n=6 each): 1h sham [SH1], 4h sham [SH4], 1h brain death [BD1], 4h brain death [BD4]. Heart rate (HR) and mean arterial pressure (MAP) were continuously monitored through a pressure transducer in the femoral artery. At the end of the experiment, bronchoalveolar lavage (BAL) was performed and biopsies were collected for histological analysis.

Results: After induction of BD there was a steep rise of HR and MAP (from 253 ± 13bpm to 452 ± 12 bpm and from 79 ± 7 mmHg to 120 ± 5.6 mmHg, respectively). A Cushing response was seen after balloon inflation characterized by a steep rise in MAP (hypertension), followed by a period of hypotension. The percentage of neutrophils were increased in [BD4] compared to [SH4] and to [BD1] (p<0.01). Differential cell count demonstrated a significant decrease in percentage macrophages in [BD4] compared to [BD1] (p<0.05). Cytokine measurement revealed a trend with increased concentration of TNF-α, IL-1β, and KC in [BD4] compared to the other groups (NS). IL-6 levels in BAL progressively increased with longer time intervals. A significant difference was found between [BD1] and [BD4] (p<0.01). On lung histology, more congestion, hemorrhage and neutrophilic infiltration was seen in [BD4], however this difference was not significant.

Conclusion: The creation of a brain death model in mice to study lung injury was successful facilitating further mechanistic studies for its treatment. A 4-hour period after brain death resulted in inflammatory changes in the lung with significant differences in differential cell count and a trend towards increased inflammatory cytokines (IL1-β, TNF-α, IL-6, and KC) in [BD4] when compared to the other groups. A longer period of BD might be needed to result in overall significant differences between groups.
Figure 1: Histological analysis of 4h of brain death (B) versus control animals (A). (x400)