## The role of PEEP in ventilation-induced lung injury: histological evidence

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**Rationale.** PEEP is usually considered protective against ventilation-induced lung injury (VILI) by reducing atelectrauma and improving lung homogeneity. Nevertheless, high PEEP levels may lead to volutrauma and reverse the effect of PEEP in lung protection. We investigated the effect of PEEP in an experimental setting, where VILI was induced through injurious mechanical ventilation at different PEEP levels.

**Methods.** We ventilated 36 healthy pigs (23.3±2.3 kg) for 50 hours with high tidal volume (equal to functional residual capacity) and high respiratory rate (30 bpm) at one of six PEEP levels – 0, 4, 7, 11, 14, 18 cmH2O – according to random allocation. At the end of the experiment, we took histological specimens representative of both lungs (Figure 1). Histological damage was expressed as the proportion of optical field in which each lesion was identified, namely edema (perivascular/alveolar), vascular congestion, inflammation, atelectasis, septal dilatation/rupture, emphysema and thrombosis.

**Results.** We found histological lung damage in all groups (Figure 2), without differences between dependent/non-dependent or apical/basal regions. Overall, the most frequent finding was vascular congestion, followed by inflammation, atelectasis and septal dilatation/rupture (Figure 2). Vascular congestion, atelectasis, inflammation and septal rupture decreased from ZEEP to 4-7 cmH2O (p<0.001) and increased again from 4-7 to 14-18 cmH2O PEEP (p<0.001). The extent of each of the remaining histological lesions – including perivascular/alveolar edema – was <10%. Consistently, lung weight and lung wet-to-dry ratios were not significantly different across PEEP groups.

**Conclusions.** The high-strain and high-rate mechanical ventilation model produced histologically relevant damage regardless of PEEP. Nevertheless, compared to ZEEP, the introduction of 4-7 cmH<sub>2</sub>O PEEP significantly blunted VILI, while PEEP increase up to 18 cmH<sub>2</sub>O led to equal or even greater damage. In our setting, low-moderate PEEP reduced atelectrauma, while higher PEEP favored volutrauma, yielding to equivalent or more severe lung damage compared to ZEEP.