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Title: Ventilator-induced lung injury in severe pneumococcal pneumonia: Protection by adrenomedullin

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Body: Ventilator-induced lung injury (VILI) contributes to mortality in ARDS. Particularly preinjured lungs are susceptible to VILI despite protective ventilation. We previously observed protection against VILI by Adrenomedullin (AM). Here we analyzed impact VILI on lung injury, pulmonary and systemic inflammation, bacterial burden and end-organ injury in established pneumonia. Further AM therapy was investigated. 24h after infection with S. pneumoniae mice were subjected to MV (12ml/kg, 6h) and AM treatment. Lung permeability, oxygenation, lung mechanics, lung and plasma cytokines and leukocytes, bacterial burden in lung, blood spleen, ALT, AST, creatinine and urine output were assessed. Expression of AM and its receptor complex (CRLR; RAMP1-3) were studied In pneumonia MV aggravated lung injury indicated by increased pulmonary permeability, oxygenation failure and worsening of lung mechanics. MV dramatically increased lung and blood cytokine levels in pneumonia, while lung leukocyte counts in pneumonia were not affected by MV. In pneumonia MV induced leukocytopenia and liver injury. Lung and blood bacterial burden was not affected by MV. MV and pneumonia increased lung AM expression. RAMP1-3 were upregulated in pneumonia but MV reduced its expression. AM protected against MV induced pulmonary hyperpermeability and deterioration of lung mechanics in pneumonia. AM did not alter inflammation but protected against VILI induced liver injury in pneumonia. MV aggravated lung injury and induced liver injury in pneumonia. MV may pave the way for progression of pneumonia towards sepsis. AM may be a promising adjuvant therapy to limit VILI in pneumonia induced ALI and may protect against end organ damage.