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Title: The effects of simvastatin in ventilator-induced lung injury

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Body: Introduction: Ventilator-induced Lung Injury Acute Lung Injury (VILI) is characterized by increased-permeability pulmonary due to excessive alveolar distention by positive-pressure mechanical ventilation. With the exception of lung-protective ventilation, no pharmacologic treatment exists. Aims: To determine the role of Simvastatin (HMGCoA reductase inhibitor) as a therapeutic agent in VILI. Methods: Adult male C57BL6 mice (n=10/group) received protective (8mL/kg) or injurious (25mL/kg) ventilation with Simvastatin (20mg/kg) starting 2 days pre- ventilation or saline intraperitoneally (ip) for four hours. Following lung mechanics' evaluation with a small animal ventilator (FlexiVent, Scireq), animals were sacrificed and bronchoalveolar lavage fluid (BALF), arterial blood and lung tissue, either snap frozen in liquid nitrogen or formalin-fixed, were obtained. Results: Simvastatin administration prevented lung injury, caused by high tidal volume ventilation (HVt). The untreated group (Un) exhibited at least a 2-fold alteration in lung mechanics values as opposed to the treated group (Tr) which maintained baseline (Bs) values (e.g.Elastance, Tr:35.22 cmH2O/ml, Un: 86.76 cmH2O/ml, Bs: 30 cmH2O/ml). Moreover drug administration attenuated inflammation as pleiocytosis and protein content in BALF were reduced (e.g.%Neutrophils in BALF, Un: 6.8% Tr: 2.7%, Bs:3%). Additionally, levels of cytokines in plasma, such as interleukine-6 and Tumor Necrosis Factor (TNF), were not altered, suggesting maintained lung integrity (TNF Un:92.95 pg/ml, Tr: 25.85 pg/ml, Bs: 30 pg/ml). Conclusions: HMGCoA reductase inhibition can reverse the pathophysiology of HVt mechanical ventilation, signifying Simvastatin as a restorative agent in VILI.