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Title: Changes of alveolar oxygen tension in chronic obstructive pulmonary disease (COPD) and effect of variable oxygen tension on hypoxia inducible factor (HIF)-1α system of alveolar epithelial cells

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Body: In COPD airway obstruction causes hypoventilated areas in the lung leading to alveolar hypoxia. HIF-1 α plays an important role in the response to hypoxia and protection of cells against harmful effects. Role of alveolar oxygen tension and HIF-1α in the development of COPD are unknown. Heathly volunteers (n=7) and 9 patients with COPD were enrolled into clinical examinations including lung function test and blood gas analysis. Mass spectrometry was used to measure exhaled O2 on the level of functional reserve capacity (FRC) and residual volume (RV). HIF1α mRNA and protein expression of alveolar epithelial cells (A549) were analyzed by RT-PCR and flow cytometry using hypoxia (FiO2: 20,9% (control); 13±1%; 6±1%; 1±1%). Exhaled O2 on the level of FRC did not change,(C:15.6±1.2 vs. COPD: 15,8±1.4 %), while on the level of RV the alveolar FiO2 was significantly decreased (C: 13,6±1,8 vs. COPD: 11.6±2.1%, $p<0.05$) in patients with COPD and the value correlated to pO2 and showed negative correlation to RV. HIF-1α mRNA and protein expression significantly increased in mild hypoxia, extreme hypoxia did not change the mRNA expression. Hypoxia significantly increased the A549 cell count in all treated groups (FiO2 13±1%: 13,33x105; FiO2 6±1%:13,2x105; FiO2 1±1%: 12,86x105 vs. control FiO2 20,9%: 7,73x105; $p<0.01$). In COPD the exhaled O2 level is decreased in parellel to hyperinflation, demonstrating that there are more severe hypoxic areas in the lungs compare to physiological conditions. Mild hypoxia increases HIF1α mRNA and protein expression, while in severe hypoxia these changes are absent.