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Title: Neuromechanical uncoupling of the respiratory system during exercise in patients with mild COPD

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Body: Increased dyspnea and physical inactivity have recently been shown to be common in patients with mild COPD. To maximize the impact of therapeutic interventions in such patients, we need to identify underlying and reversible mechanisms of activity limitation. Accordingly, the purpose of this study was to elucidate the physiological abnormalities of the respiratory system and its central controller during exercise in mild COPD compared to healthy controls. Following a familiarization visit, participants (COPD: n=16 (8M:8F), post-β_2 agonist FEV_1/FVC=63% and FEV_1=93%pred; controls, n=16 (8M:8F)) performed an incremental cycle test while detailed metabolic, ventilatory, sensory, and respiratory mechanical responses were obtained. Diaphragmatic EMG (EMGdi) was measured using a multi-pair electrode catheter. Neuromechanical uncoupling (NMU) of the respiratory system was calculated as the ratio between EMGdi (%max) and tidal volume (%pred vital capacity (VC)). Patients with mild COPD had a reduced inspiratory capacity and increases in ventilation, EMGdi, and NMU vs. controls (fig.1). Dyspnea-ventilation slopes were strongly correlated with the degree of NMU in mild COPD ($r=0.833, P<0.0001$) but not in health ($r=0.387, P=0.139$). Interventions such as exercise training that can reduce ventilatory requirements and central respiratory drive are likely to meaningfully reduce dyspnea and improve exercise tolerance in mild COPD.