Sedation-Ventilation Interactions in Spontaneously Breathing Patients with Acute Hypoxemic Respiratory Failure

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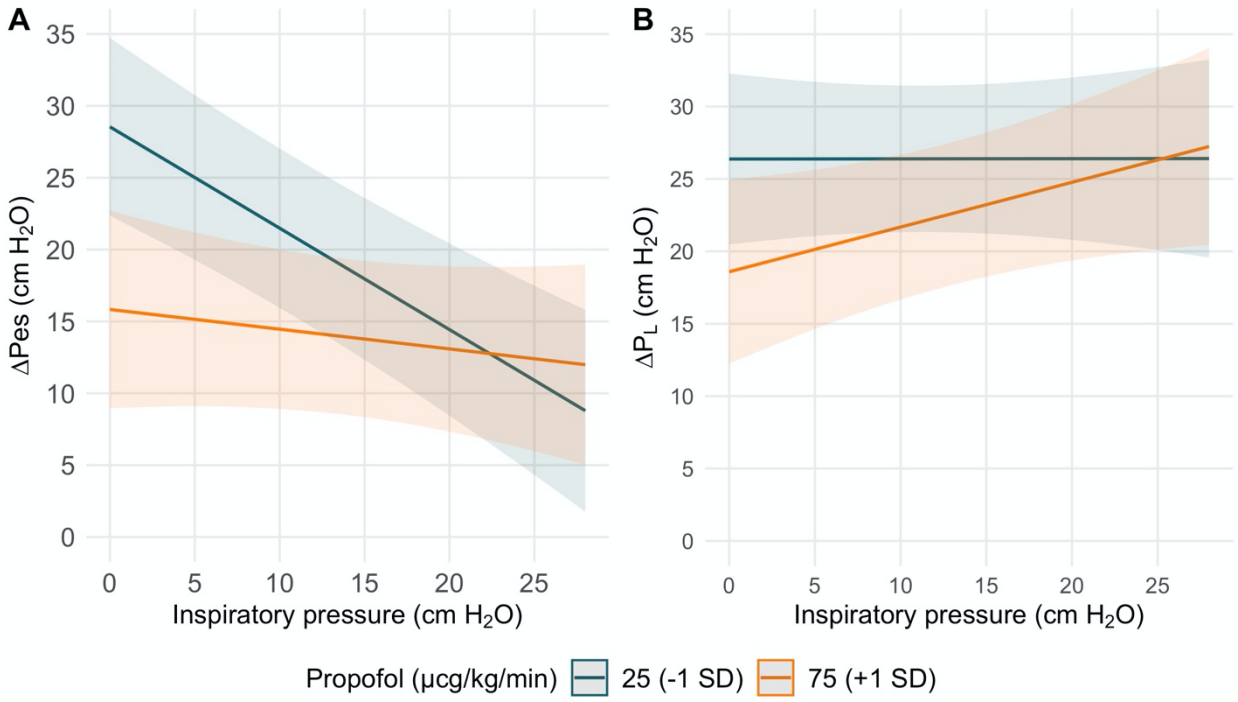
Background:
A strategy combining titration of inspiratory pressure, PEEP, and sedation can facilitate lung and diaphragm protection in patients with acute hypoxemic respiratory failure (AHRF). However, the individual effects of each of these interventions on respiratory effort and lung distending pressure, and their potential interactions, have not been described.

Methods:
Secondary analysis of the LANDMARK trial, a study that evaluated the physiologic effects of a lung- and diaphragm-protective ventilation and sedation strategy in patients with AHRF (n=30). Respiratory effort (quantified by the absolute value of the esophageal pressure swing, |ΔPes|) and lung distending pressure (quantified by the dynamic driving transpulmonary pressure, $\Delta P_{L,dyn}$) were measured at baseline and after changes in inspiratory pressure, PEEP, and sedative dose. We used mixed effects linear regression to evaluate the effect of these changes on ΔPes and $\Delta P_{L,dyn}$. The models included interaction terms between the independent variables to assess for effect modification. We also evaluated the association between individual patient characteristics and ΔPes and $\Delta P_{L,dyn}$. In patients receiving VV-ECMO, we conducted a mediation analysis to evaluate the potential effect of ventilatory ratio as a mediator of the effect of sweep gas flow on ΔPes.

Results:
Increasing inspiratory pressure attenuated |ΔPes| (-1 cm H_2O, 95% CI -1.5, -0.5 cm H_2O) but not $\Delta P_{L,dyn}$ (0 cm H_2O, 95% CI -0.5, 0 cm H_2O). Increasing propofol attenuated both |ΔPes| (-2.5 cm H_2O, 95% CI -3, -1.5 cm H_2O) and $\Delta P_{L,dyn}$ (-1.5 cm H_2O, 95% CI -2, -1 cm H_2O). The effect of inspiratory pressure on |ΔPes| and $\Delta P_{L,dyn}$ varied according to the propofol dose (p-value <0.001 for interactions, Figure). Elastance and ventilatory ratio were associated with higher |ΔPes|, and this effect was larger at higher values of each variable (p-value for interaction= 0.02). VV-ECMO was associated with lower |ΔPes| (-10 cm H2O, 95% CI -18, -3 cm H_2O). The effect of propofol on |ΔPes| varied between patients receiving VV-ECMO and those not on VV-ECMO (p-value for interaction <0.001). In mediation analysis, ventilatory ratio mediated the effect of sweep gas flow on ΔPes (average mediated proportion= 0.61).

Conclusions:
Patients with higher elastance and ventilatory ratio exhibited greater respiratory effort. Higher inspiratory pressure, higher propofol dose, and application of VV-ECMO were associated with lower respiratory effort. However, there are complex interactions between these interventions. In patients receiving higher propofol infusion rates, increasing inspiratory pressure increased lung distending pressure without reducing respiratory effort. Patients receiving VV-ECMO required significantly lower propofol dose to control respiratory effort.

Figure. Moderating effect of propofol on inspiratory pressure



The effect of inspiratory pressure on ΔPes and $\Delta P_{L,dyn}$ varied according to the propofol dose. Increasing inspiratory pressure substantially attenuated ΔPes in patients receiving lower propofol dose (Panel A), leading to a net neutral effect on $\Delta P_{L,dyn}$ (Panel B). Conversely, the effect of inspiratory pressure on ΔPes was minimal in patients already receiving higher propofol dose (Panel A); in these patients, $\Delta P_{L,dyn}$ substantially increased when inspiratory pressure was increased (Panel B).