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CORRESPONDENCE

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Mechanisms of lung and diaphragmatic protection by high PEEP in obese COVID-19 ARDS: role of the body mass index

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To the Editor:

Obesity increases the risk of requiring mechanical ventilation (MV) and developing acute respiratory distress syndrome (ARDS) in patients with coronavirus 2019 (COVID-19) [1].

Spontaneous breathing (SB) may potentially compromise lung and diaphragmatic protection in COVID-19-induced ARDS [2]. In recruitable models, high positive end-expiratory pressure (PEEP) was shown to render SB less injurious [3]. Nonetheless, the effects of high PEEP have been scarcely studied in clinical scenarios. Previous literature suggests that obese subjects might benefit from higher PEEP and these positive effects might be proportional to the obesity grade [4, 5].

We assessed whether the beneficial effects of high PEEP on lung and diaphragmatic protection depend on body mass index (BMI) in intubated obese patients recovering from COVID-19-associated ARDS.

This is an exploratory analysis of a physiological study conducted at Sanatorio Anchorena San Martín, Argentina. Consecutive adults with COVID-19-associated ARDS, BMI > 30 kg/m^2, intubation > 48 hs and SB in pressure support for > 2 hs were included.

The pressure support level was titrated by the attending physician. Esophageal pressure (P_{es}) was measured with an air-filled (1 mL) esophageal balloon (MBMed®-BA-A-008, non-latex) according to manufacturer recommendations after balloon's correct positioning. Airway pressure, flow, volume and P_{es} were recorded by a dedicated system (FluxMed, MBMed®).

Our primary endpoints were the changes in muscular pressure (P_{mus}), pressure–time product per-minute (PTP_{min}) and dynamic driving transpulmonary pressure (ΔPL_{dyn}) from low-to-high PEEP and its correlation with BMI. Data were collected 10 min after changing PEEP (5–15cmH$_2$O). Respiratory variables averages were computed based on respiratory cycles of the last 30–60 s of each PEEP step considered stable. In 16/21 patients, chest wall elastance (E_{cw}) was assessed before SB was present. In the remaining, E_{cw} was measured applying a hyperventilation maneuver by increasing the pressure support until observing positive P_{es} deflections. All traces were analyzed using Biopac Student Lab PRO®.

Correlations were performed with Spearman's rank test. To assess the differential effects of high PEEP, we analyzed subgroups based on a commonly used BMI cut-off (≥ 35 kg/m^2) [4]. A linear mixed-effects regression model for repeated measures was fitted to assess interaction between PEEP (5–15cmH$_2$O) and BMI (≥ or < 35 kg/m^2). *P* values were adjusted by post hoc Tukey's correction. A two-tailed $P \leq 0.05$ was considered statistically significant. Data were analyzed with R4.0.3 software.

We studied 21 patients (age, median [IQR, 25th–75th]: 56 years [IQR, 51–67]; BMI: 34.3 kg/m^2 [IQR, 31.6–40.4]). At admission, 85% had moderate ARDS and 3 had mild ARDS. All the patients required neuromuscular blockers and 62% received prone ventilation.

At inclusion, the patients had 5 MV days [IQR, 3–7] and remained ventilated for additional 11 days [IQR, 5–20].

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The PaO_2/FiO_2 was 214 mmHg [IQR, 183–252], pressure support was 8cmH_2O [IQR, 5–10], and inspired oxygen was 0.40 [IQR, 0.35–0.50]; the Richmond Agitation–Sedation Scale was − 3 to − 4.

The BMI significantly correlated with changes in P_{mus}, PTP_{min} and ΔPL_{dyn} (Fig. 1-A) We found an interaction between BMI and PEEP regarding to changes in P_{mus} ($F_{(1,19)=}$6.2;P=0.022), PTP_{min} ($F_{(1,19)=}$7.4, P=0.013) and ΔPL_{dyn} ($F_{(1,19)=}$10.4, P=0.004). Only the subgroup with BMI ≥ 35 reduced the P_{mus} (mean difference (95%CI): − 3.3cmH_2O (− 1.5 to − 6.1)), PTP_{min} (− 94.5 cmH_2O.s/min(− 23.3 to − 165.7)) and ΔPL_{dyn} (− 3.2cmH_2O(− 1.6 to − 5.7)) with high PEEP (Fig. 1-B). The results remained significant after excluding an outlier from the severely obese subgroup. In these patients (BMI ≥ 35), the end-expiratory transpulmonary pressure (PL_{exp}) was more negative at low PEEP and became closer to 0cmH_2O at high PEEP (Fig. 1-C). The optimization of lung–diaphragmatic protection was explained by reduction of PTP-associated components, improvement in dynamic lung compliance (CL_{dyn}), neuromuscular ventilatory coupling and respiratory drive (Fig. 1-D).

We demonstrate that the obesity grade greatly influences the beneficial effects of PEEP on relevant monitoring variables directly linked to the lung and diaphragmatic protection.

In obese subjects, the increased pleural pressure may reduce end-expiratory lung volume and become PL_{exp} negative, causing atelectasis and airway closure [4, 5]. Alveolar and airways collapse may alter ventilation distribution and cause occult pendelluft, resulting in local/global overdistension [3]. This might impose higher loads on the respiratory muscles, jeopardizing the SB even more [5].

Our findings indicate that these pathological mechanisms may play a role during SB in obese COVID-19 ARDS patients and can be counteracted by PEEP [4, 5]. Nonetheless, despite fulfilling obesity criteria (BMI > 30 kg/m^2), not all patients benefited from high PEEP. Accordingly, the least obese subgroup did not experience work of breathing unloading and deteriorated lung mechanics, neuroventilatory coupling and respiratory drive, suggesting that lung overdistension was probably induced. In this context, we suggest that P_{es} should be used to titrate PEEP during assisted ventilation to avoid the potential harms associated with unnecessarily high PEEP levels, taking a slightly positive PL_{exp} as a reasonable target [4].

Our study is mainly limited by the small sample size and the lack of direct measurements of lung–diaphragmatic injury. Additionally, PEEP steps were not random and the time spent during each PEEP level was short.

In summary, considering the complexity of SB in COVID-19-induced ARDS [2], high PEEP might be considered as a potentially useful tool to provide lung and diaphragmatic protection particularly in selected individuals with BMI ≥ 35 kg/m^2, where the obesity-associated mechanical alterations might be specially exacerbated.

(See figure on next page.)

Fig. 1 **A** Correlation between BMI and changes (%) in P_{mus}, PTP_{min}, and ΔPL_{dyn}; **B** P_{musc} (upper), PTP_{min} (middle) and ΔPL_{dyn} (lower) with PEEP 5 and 15cmH_2O; **C** end-expiratory transpulmonary pressure at PEEP 5 and 15cmH_2O; **D** mean (95% CI) percentage of change in PTP-associated components (intrinsic PEEP, resistance, elastance), dynamic lung compliance (CL_{dyn}), neuromuscular ventilatory coupling expressed as tidal volume-to-pressure–time product per breath (VT/PTP_{breath}) and intensity of respiratory drive expressed as esophageal pressure to neural inspiratory time (P_{es}/Ti). In panels **B**, **C** and **D**, the patients are divided in subgroups according to BMI < 35 kg/m^2 (n = 12; median BMI 31.8 [IQR, 30.7–33.3] kg/m^2) and ≥ 35 kg/m^2 (n = 9, median BMI 43.6 [IQR, 38.5–48.9] kg/m^2)

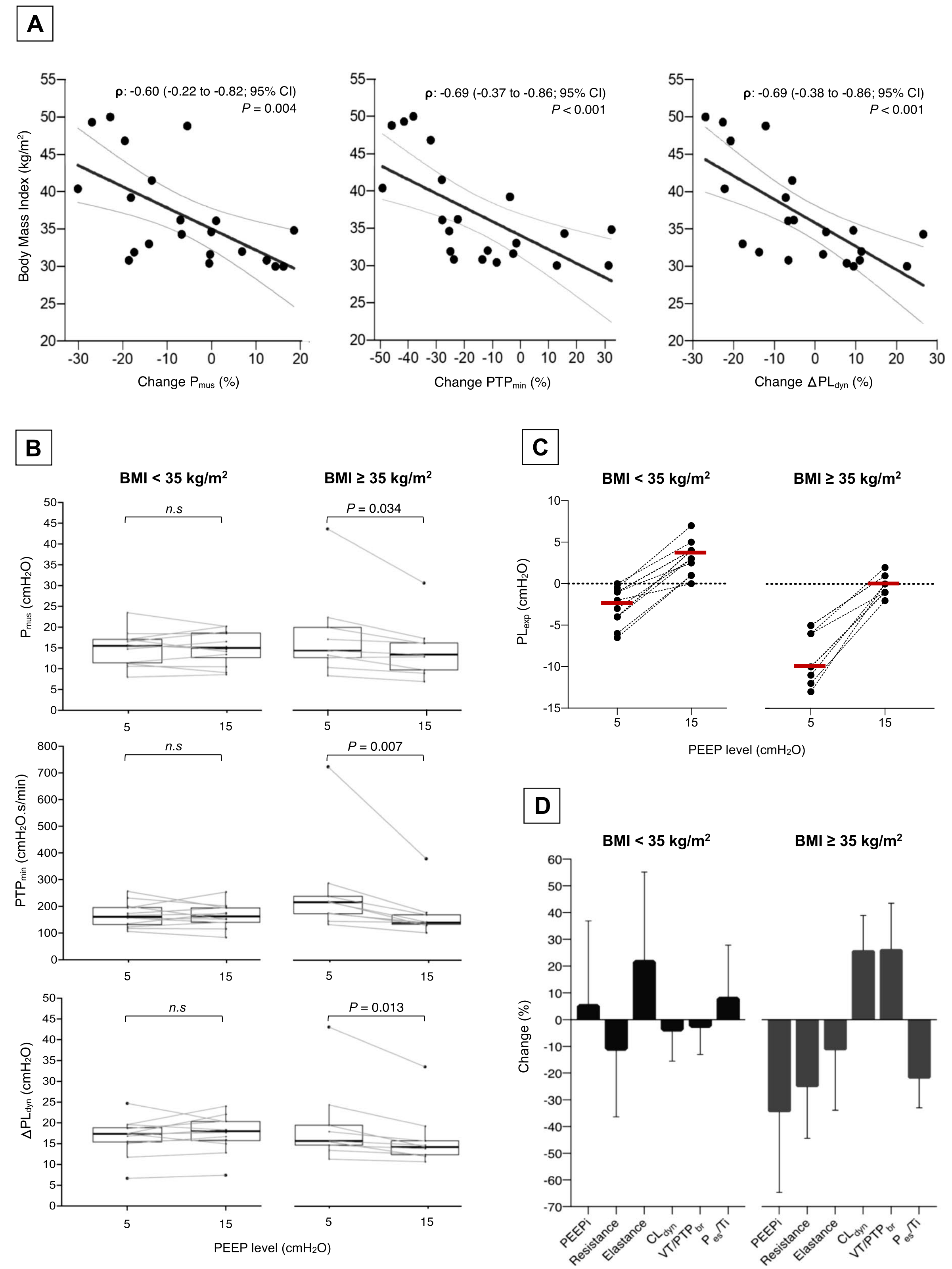

Fig. 1 (See legend on previous page.)

Abbreviations

MV: Mechanical ventilation; ARDS: Acute respiratory distress syndrome; COVID-19: Coronavirus disease 2019; SB: Spontaneous breathing; PEEP: Positive end-expiratory pressure; BMI: Body mass index; P_{es}: Esophageal pressure; P_{mus}: Muscular pressure; PTP_{min}: Pressure–time product per minute; ΔPL_{dyn}: Peak dynamic driving transpulmonary pressure; PaO_2/FiO_2: Arterial oxygen pressure to inspired oxygen; P_{es}/Ti: Esophageal pressure to neural inspiratory time; VT/PTP_{breath}: Tidal volume-to-pressure–time product per breath; CL_{dyn}: Dynamic lung compliance; n.s: No statistically significant; IQR: Interquartile range.

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Author contributions

J.P., J.H.D, M.A. and E.N. contributed to the study concept and design. J.P., J.H.D and M.A. contributed to the acquisition of data. J.P., J.H.D, M.A., E.N. and C.C.A.M. contributed to the analysis and interpretation of data. J.P., J.H.D, M.A., E.N. and C.C.A.M. contributed to drafting the manuscript and critically revising the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The original protocol was approved by the Institutional review board (approval #08-2019) and registered in ***clinicaltrials.gov*** (NCT04524091). The informed consent was obtained from the patient's next of kin.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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