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Title: The biological impact of different transpulmonary pressures during mechanical ventilation in experimental acute respiratory distress syndrome

Ms. Cynthia 662 Samary cynthiasamary@gmail.com [1], Ms. Raquel 663 Santos rss.quelzinha@gmail.com [1], Dr. Cíntia 664 Santos cintialsvet@gmail.com [1], Ms. Nathane 668 Félix nathanefelix@gmail.com [1], Ms. Maíra 669 Ramos mairamos7@gmail.com [1], Prof. Dr Cristiane 667 Baez-Garcia crisbaezgarcia@gmail.com [1], Dr. Pedro 670 Silva pedroleme@gmail.com [1], Prof. Paolo 665 Pelosi ppelosi@hotmail.com [2] and Prof. Dr Patricia 666 Rocco prmrocco@gmail.com [1]. [1] Carlos Chagas Filho Biophysics Institute, Federal University of Rio de Janeiro, Rio de Janeiro, Rio de Janeiro, Brazil, 21931560 and [2] IRCCS AOU San Martino-IST, Department of Surgical Sciences and Integrated Diagnostics, University of Genoa, Genoa, Italy .

Body: Low tidal volume (V_T) and plateau pressure of the respiratory system (Pplat,rs) have become the cornerstone of protective mechanical ventilation in acute respiratory distress syndrome (ARDS) patients, reducing ventilator-associated lung injury (VALI). However, the key variable in determining pulmonary overdistension is delta transpulmonary pressure (ΔP,L). Since, the importance of V_T versus PEEP as VALI determinants remains controversial, we investigated the effects of different ΔP,L generated by the combination of V_T and PEEP in experimental ARDS. Wistar rats received Escherichia coli lipopolysaccharide intratracheally. After 24h, rats were randomized into groups according to ΔP,L: low (7.5cmH2O), mean (10cmH2O), or high (12cmH2O). Different combinations of V_T and PEEP were applied: ΔP,Llow (V_T=6ml/kg, PEEP=3cmH_2O); ΔP,Lmean (V_T=6ml/kg, PEEP=9.5cmH_2O or V_T=13ml/kg, PEEP=3cmH_2O); ΔP,Lhigh (V_T=6ml/kg, PEEP=11cmH_2O or V_T=20ml/kg, PEEP=3cmH_2O), during 1h. ΔP,Llow led to alveolar collapse and deterioration in gas exchange. Conversely, ΔP,Lmean with PEEP=9.5 cmH_2O yielded alveolar hyperinflation and higher expression of markers related to hyperinflation [Amphiregulin and type III procollagen (PCIII)], inflammation (IL-6) and damage inflicted to type I pneumocyte (RAGE). In the ΔP,Lhigh groups, higher PEEP resulted in alveolar hyperinflation but PCIII, IL-6 and RAGE were lower compared to ΔP,Lmean with PEEP=9.5cmH_2O whereas amphiregulin expression remained elevated. In conclusion, our results suggest that the smallest dynamic alveolar inflation preserved the integrity of the barrier reducing VALI.