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EDITORIAL

Finding the optimal tidal volume in acute respiratory distress syndrome

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Severe hypoxemia, alveolar infiltrates associated to increased permeability, and histological damage due to lung inflammation constitute the key elements of the conceptual model of acute respiratory distress syndrome (ARDS). While tidal volumes (V_T) of 12–14 ml/kg and end-inspiratory plateau pressures (P_{PLAT}) up to 50 cmH_2O were initially used to "normalize" arterial blood gases [1], experimental and clinical studies performed in the last 20 years consistently demonstrated that such ventilatory approaches worsened lung damage (ventilator-induced lung injury, VILI) [2]. The seminal trial performed by the ARDS Network showed that, compared to a traditional "high V_T" (12 ml/kg predicted body weight, PBW), the use of a "low V_T" (6 ml/kg PBW) significantly reduced mortality from 40% to 31% [3]. Consequently, 6 ml/kg normalized to PBW has been established as the standard V_T for patients with ARDS (Fig. 1). Although the range of 6–8 ml/kg PBW is acknowledged as the standard [4], various factors question the use of 6 ml/kg PBW as a fixed cut-off.

First, at the moment there are no clinical studies that have evaluated whether the influence on outcomes of V_T of 6 ml/kg is equivalent, better, or worse compared to the effects associated with V_T ranging from 7 to 11 ml/kg [5, 6]. Second, a recent meta-analysis informing the current guidelines showed that, although being recommended by experts, "lower V_T" (i.e., 4–8 ml/kg PBW) does not have a significant effect size on patient outcome [5]. It should be emphasized that this meta-analysis was performed including only three trials (the ARDS Network study and two smaller trials), and its heterogeneity was moderate-high (I^2 61%). Third, a significant number of patients ventilated with "low V_T" still exhibit signs of hyperinflation [7]. Fourth, setting V_T based on "milliliters per kilogram of PBW" in order to normalize it to lung size might be misleading [8, 9], since this approach overlooks the fact that the proportion of lung available for ventilation is significantly decreased in ARDS. In alternative, V_T may be scaled to the aerated portion of the lung as estimated by the compliance of the respiratory system (C_{RS}). Amato and coworkers proposed driving pressure ($\Delta P = V_T/C_{RS}$) as the most accurate "ventilator predictor" of outcome in patients with ARDS and demonstrated that the favorable effects of randomly assigned reductions in V_T were largely mediated by the decrease in ΔP [8].

A simplified reading of these arguments may lead to the suggestion that V_T should be set to optimize ΔP and C_{RS} (i.e., the elastic components of mechanical power contributing to VILI) [11]. Nevertheless, in our view, all the above discussed arguments raise two still unresolved questions: (a) Is ΔP an indicator of unsafe V_T and does it have a direct impact on the outcome? (b) What factors can influence C_{RS} and the interplay between V_T and ΔP? Addressing these issues is crucial for clinicians to tailor V_T, enhance mechanical ventilation, and minimize the potential risk for VILI.

(a) *Is ΔP an indicator of unsafe V_T and does it have a direct impact on the outcome?*
ΔP was originally proposed as the ventilation variable that best stratifies the risk of hospital death [8]. More recently, an emulated randomized trial based on registry of invasively and non-invasively ventilated patients showed that the 30-day ventilatory mortality was 20.1%. A 1.9% and 4.4% reduction of the absolute risk of 30-day ventilator mortality was shown for $\Delta P < 15$ and < 10 cmH_2O, respectively [10].

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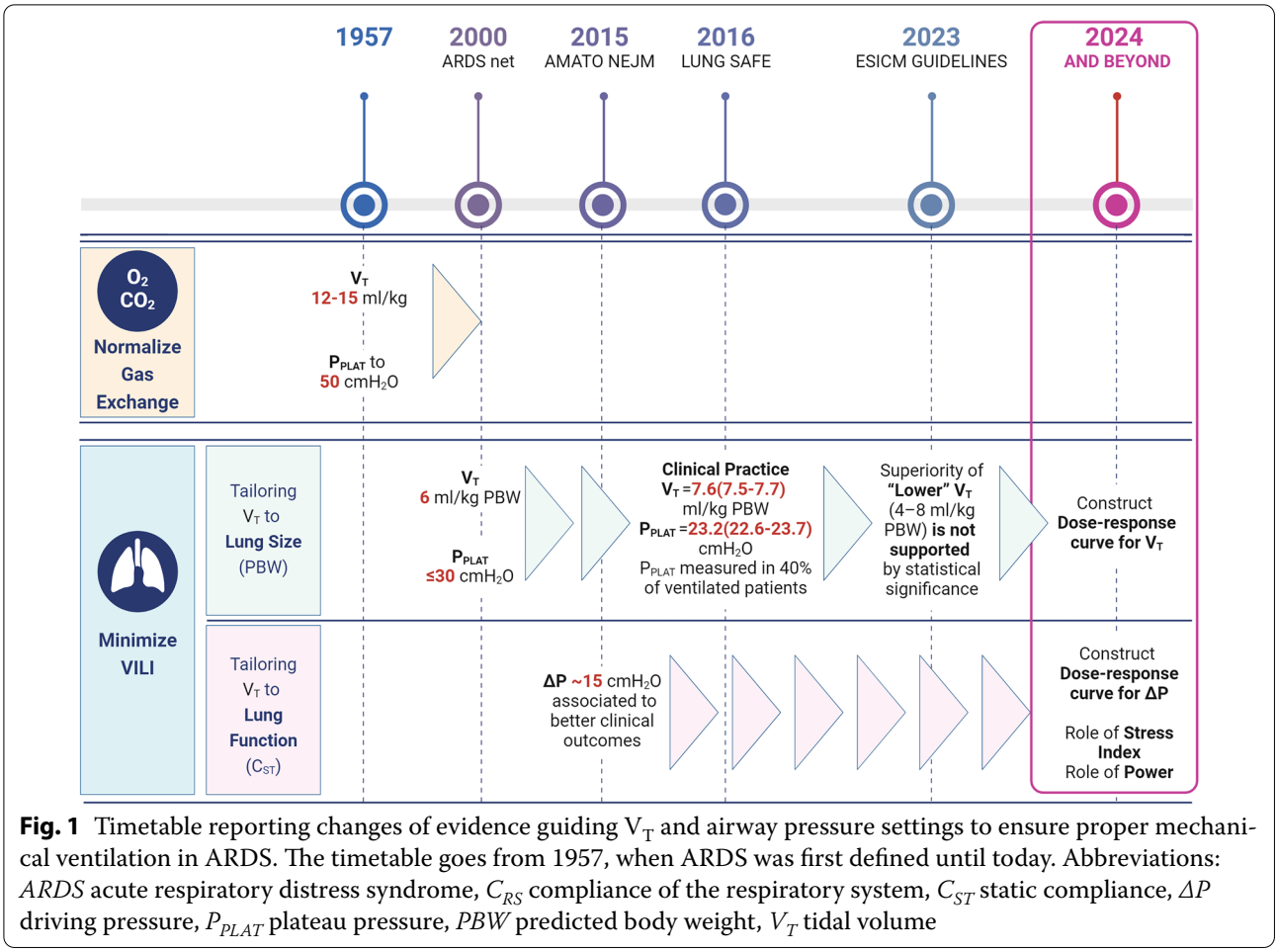

Fig. 1 Timetable reporting changes of evidence guiding V_T and airway pressure settings to ensure proper mechanical ventilation in ARDS. The timetable goes from 1957, when ARDS was first defined until today. Abbreviations: *ARDS* acute respiratory distress syndrome, C_{RS} compliance of the respiratory system, C_{ST} static compliance, *ΔP* driving pressure, P_{PLAT} plateau pressure, *PBW* predicted body weight, V_T tidal volume

This may be especially true when ΔP is limited at the very onset of mechanical ventilation and for a longer ventilation time [11]. Interestingly, ΔP was shown to be correlated to mortality if calculated statically (i.e. using in the calculation end-inspiratory plateau pressure) or dynamically (i.e. using in the calculation peak-inspiratory pressure) [10, 11]. Although a recent trial failed to support the use of $V_T < 6$ ml/kg PBW when implemented with extracorporeal CO_2 removal [12], the absence of lower safe limits still encourage further studies to evaluate the clinical efficacy of "ultra-protective" ventilation [13].

(b) *What factors can influence C_{RS} and the interplay between V_T and ΔP?*

The level of positive end-expiratory pressure (PEEP) selected by the clinician as well as the elastic components of the chest wall (chest wall elastance: E_{CW}) have an important influence on C_{RS}, and on the interplay between V_T and ΔP. Under these circumstances, the component of mechanical stress imputable to (a) lung volume (as influenced by the level of applied PEEP) and (b) to the partitioning of respiratory mechanics between chest wall and lung components (as assessed by measurement of E_{CW}) may both affect C_{RS} and ΔP for a given V_T [2]. Clinical trials comparing high vs low PEEP did not target a limited ΔP strategy, whereas studies testing physiology-guided protocols to set PEEP used different methodologies (e.g., aiming at end-expiratory transpulmonary pressure of zero, or at the highest C_{RS} following or not lung recruitment) [5]. Moreover, several other uncontrolled factors may contribute to the variable effects of ΔP and PEEP optimization. They include severity and pattern of injury, body positioning, airway closure and hemodynamic and the non-homogeneous distribution of ventilation makes regional stress not necessarily mirrored by a single values of ΔP and/or C_{RS} [7]. In this context, stress index (describing the changes in compliance with tidal inflation), lung imaging technique (e.g., electric impedance tomography and computed tomography) and estimation

of pleural pressure, may guide personalized ΔP and PEEP setting aiming at a more homogeneous distribution of ventilation and regional lung mechanics [14].

Take-home message

The ARDS Network study was the seminal study introducing the concept of protective mechanical ventilation. However, a fixed V_T cut-off (6 ml/kg PBW) has been recently questioned [9–11]. New evidence suggests that it may be more advantageous to optimize V_T considering ΔP. Regional distribution of volumes and regional lung mechanics may be the missing factor, although not demonstrated on a large scale. While waiting for more research on the topic, clinicians must continue using the concept of protective ventilation considering the multifactorial contribution of ΔP, C_{RS}, E_{CW}, PEEP, and regional lung mechanics, to individualize V_T.

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Declarations

Conflicts of interest

The authors declare that they have no conflict of interest.

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