REVIEW

Should we use driving pressure to set tidal volume?

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Purpose of review

Ventilator-induced lung injury (VILI) can occur despite use of tidal volume (V_T) limited to 6 ml/kg of predicted body weight, especially in patients with a smaller aerated compartment (i.e. the baby lung) in which, indeed, tidal ventilation takes place. Because respiratory system static compliance (C_{RS}) is mostly affected by the volume of the baby lung, the ratio V_T/C_{RS} (i.e. the driving pressure, ΔP) may potentially help tailoring interventions on V_T setting.

Recent findings

Driving pressure is the ventilatory variable most strongly associated with changes in survival and has been shown to be the key mediator of the effects of mechanical ventilation on outcome in the acute respiratory distress syndrome. Observational data suggest an increased risk of death for patients with ΔP more than 14 cmH_2O, but a well tolerated threshold for this parameter has yet to be identified. Prone position along with simple ventilatory adjustments to facilitate CO_2 clearance may help reduce ΔP in isocapnic conditions. The safety and feasibility of low-flow extracorporeal CO_2 removal in enhancing further reduction in V_T and ΔP are currently being investigated.

Summary

Driving pressure is a bedside available parameter that may help identify patients prone to develop VILI and at increased risk of death. No study had prospectively evaluated whether interventions on ΔP may provide a relevant clinical benefit, but it appears physiologically sound to try titrating V_T to minimize ΔP, especially when it is higher than 14 cmH_2O and when it has minimal costs in terms of CO_2 clearance.

Keywords

extracorporeal CO_2 removal, plateau pressure, respiratory mechanics, stress and strain, tidal volume, ventilator-induced lung injury

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a frequent disease that affects up to 23% of mechanically ventilated patients over the course of the ICU stay [1▪▪]. Lungs with ARDS are characterized by different degrees of aeration loss and can be modeled in two regions of various dimensions; one normally aerated, in which tidal ventilation occurs and thus responsible for the mechanical forces and pressures observed in the patients (i.e. the so called 'baby lung'); the other consolidated or collapsed, not contributing to gas exchange, still perfused and causing the oxygenation impairment by a shunt mechanism [2]. Mechanical ventilation is the cornerstone life-saving treatment of ARDS, and settings aimed at trying to partially restore the loss in aerated lung volume and reverse oxygenation impairment. Nevertheless, mechanical ventilation is mostly delivered in a small lung and can itself aggravate and even initiate lung injury through the so-called ventilator-induced lung injury (VILI), described as a dysregulated inflammatory response with a systemic dissemination (biotrauma) driven by

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KEY POINTS

- Driving pressure, defined as the ratio of tidal volume to respiratory system compliance, is a bedside available tool to estimate lung dynamic strain.
- Driving pressure is the ventilatory variable most strongly associated to changes in survival: driving pressure more than 14 cmH_2O during ARDS seems at risk of higher mortality.
- Although not demonstrated in prospective studies, titrating tidal volume to reduce driving pressure appears physiologically reasonable, but a well tolerated value to be achieved is not known.
- Prone position and simple ventilatory adjustments to enhance CO_2 clearance can help reduce driving pressure in isocapnic conditions.
- The feasibility and safety of low-flow extracorporeal CO_2 removal to further reduce tidal volume and driving pressure are currently under investigation.

pressure (barotrauma) and volume (volutrauma) overload [3].

To determine the best balance between the benefit of providing life support and the risks of mechanical ventilation, the last decades have witnessed a great effort in identifying strategies to limit VILI in ARDS and beyond: in 2000, a protective ventilation strategy providing tidal volume (V_T) of 6 ml/kg of predicted body weight (PBW) was shown to improve survival as compared to a higher, traditional V_T approach (12 ml/kg PBW) [4]. However, there is convincing evidence that patients with a small aerated compartment available for ventilation can still suffer from VILI even though V_T is limited to 6 ml/kg PBW [5]. Although static strain describes the tissue deformation generated by a given pressure, dynamic strain was suggested to better assess the tissue distortion and the risk of VILI because of V_T [6]. Dynamic strain is computed as the ratio of V_T to functional residual capacity: unfortunately, assessment of functional residual capacity may not be clinically feasible, limiting its use to the research field [7].

Recently, the driving pressure (ΔP) has been proposed as a bedside available tool to surrogate dynamic strain during mechanical ventilation.

In the present manuscript we will discuss the physiological meaning of ΔP and its possible application in titrating V_T in patients with ARDS.

PHYSIOLOGIC MEANING OF DRIVING PRESSURE

Because the ratio of respiratory system compliance (C_{RS}) to the healthy lung available for ventilation seems to be relatively constant [2], reduction in C_{RS} has been advocated as a tool to grossly estimate the volume of functional residual capacity. Amato *et al.* recently hypothesized that the impact of tidal ventilation could be better assessed if V_T was normalized to C_{RS} rather than to PBW, proposing the ratio V_T/C_{RS} to surrogate lung dynamic strain. This ratio was named airway driving pressure (ΔP) and can be easily calculated at the bedside as airway plateau pressure minus positive end-expiratory pressure ($\Delta P = P_{plat} - PEEP$) [8■■].

Airway driving pressure is the pressure needed to overcome the elastic recoil of the respiratory system (respiratory system elastance, E_{RS}) as V_T is inflated. Importantly, although P_{plat} represents the total amount of pressure delivered through both PEEP and V_T, ΔP only reflects the pressure load because of tidal ventilation. It is interesting to note that such approach seems physiologically sound to assess the risk of VILI, because higher PEEP does not necessarily contribute to lung injury and can even mitigate it and contribute to survival [9], despite increasing P_{plat} [6].

Airway driving pressure is the sum of the pressure overcoming the elastance of the lung (E_L) and of the chest wall (E_{CW}): accordingly, the portion of ΔP pressure distending the lung is called lung driving pressure (ΔP_L) and can be directly measured as

$$\Delta P_L = (P_{plat}\text{-}Pes_{end\text{-}insp}) - (Peep\text{-}Pes_{end\text{-}exp})$$

or computed as

$$\Delta P_L = \Delta P \times (E_L/E_{RS}),$$

where P_{plat} represents airway plateau pressure, $Pes_{end\text{-}insp}$ esophageal pressure at end inspiration, Peep airway pressure at end expiration and $Pes_{end\text{-}exp}$ esophageal pressure at end expiration (Fig. 1).

Although P_{plat} measured at the end of a 0.3 s inspiratory hold is reliable to correctly compute ΔP and ΔP_L, intrinsic PEEP should be carefully measured during an end-expiratory hold and total PEEP used in the calculations; the use of set PEEP to approximate total PEEP can overestimate both ΔP and ΔP_L as intrinsic PEEP is present. In Amato's validation study, set PEEP was used to compute ΔP and ΔP_L, as it is more easily available from large datasets [8■■]. It is also important to keep in mind that in some situations like airway closure, the airway pressure may not represent alveolar pressure [10]. We do not know the prevalence of this problem in ARDS, but it has been well described in obese patients. Finally, during pressure controlled ventilation, the peak pressure is frequently used as a surrogate for the plateau pressure, which, however, is only an approximation [11].

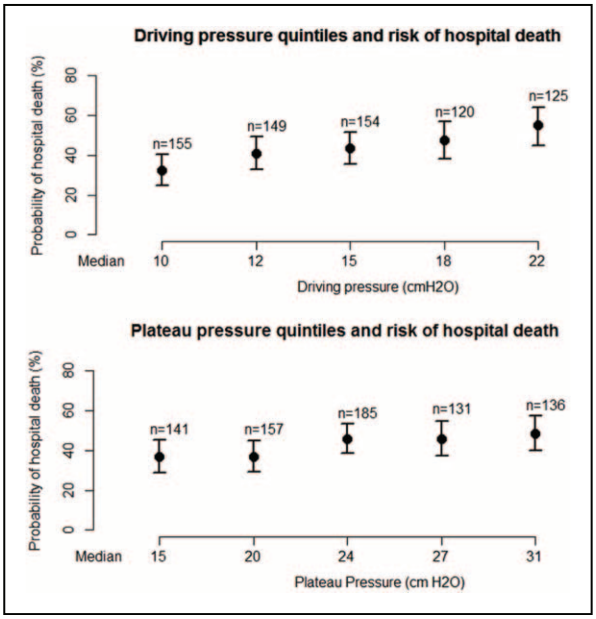

FIGURE 1. Driving pressure and survival. Quintiles of driving pressure and survival. Plateau pressure quintiles are tabled for comparison. Please note the linear relationship between quintiles of driving pressure and mortality. Reproduced from [1▪▪].

DRIVING PRESSURE DURING PASSIVE VENTILATION

To determine and weight the relative effects on survival of changes in variables of interest such as ΔP, V_T, V_T/PBW, P_{plat}, and PEEP in the very early phase of the disease, Amato *et al.* recently conducted a mediation analysis combining individual data from 2365 individuals involved in randomized trials comparing ventilation strategies in patients with ARDS. Mediation analysis is a statistical approach that allows to determine if a specific variable, although strongly affected by treatment-group assignment, has an effect on outcome that explains in whole or in part the effects resulting from treatment-group assignment [8▪▪]. The results showed that a lower ΔP was the ventilator variable the most strongly associated to improved clinical outcome; any change in V_T, V_T/PBW, P_{plat}, and PEEP affected clinical outcome only when modifying ΔP, which appeared to be the strongest mediator of the effects of all ventilator settings on survival. Impressively, changes in P_{plat} led to improved survival when associated to a lower ΔP, did not modify clinical outcome in case of unchanged ΔP and worsened mortality if resulting in any ΔP increase. Similarly, with stable P_{plat}, the effect of V_T setting on patients' survival existed only when rescaled to C_{RS} ($V_T/C_{RS} = \Delta P$), whereas lower absolute values of V_T did not improve outcome if ΔP remains unchanged.

The importance of ΔP in determining the effects of ventilator settings has been subsequently confirmed by a recent epidemiological study involving more than 2000 patients with ARDS in 50 countries [1▪▪]: higher survival was detected in patients with $\Delta P \leq 14$ cmH_2O at the very onset of the syndrome. In addition, a linear relationship between quintiles of ΔP and ICU mortality was documented (Fig. 1 [1▪▪]), thus hypothesizing that, although $\Delta P > 14\,cmH_2O$ can predict a worse outcome, a well tolerated threshold for such parameter is yet to be identified. It must be noted that the design of the study, aiming at describing ARDS management in a wide variety of institutions and outside the procedures of rigorously designed clinical trials, corroborates the relevance, the external validity, and the reproducibility of the 'driving pressure approach' in the clinical setting.

ΔP is affected by E_{CW}, which may vary among patients. Hence, driving pressure partitioning to evaluate ΔP_L may be necessary to rigorously assess the pressure distending the lungs independently from the effects of E_{CW}. Chiumello *et al.* recently reported that ΔP_L and ΔP are closely related and that both are associated with changes in lung stress, defined as the total increase in transpulmonary pressure because of PEEP and tidal volume. Contrarily, lung stress was not predicted by set V_T nor by V_T/PBW. Notably, they identified $\Delta P_L > 11.7\,cmH_2O$ and $\Delta P > 15\,cmH_2O$ as equipotent threshold values to detect high lung stress (i.e. $>24\,cmH_2O$) [12▪].

Very few available data clarify the respective roles of ΔP and ΔP_L in determining outcome, because data from advanced monitoring with esophageal pressure are not always available in large datasets. In a cohort of 69 patients with ARDS, we could not find any difference between ΔP_L and ΔP in predicting survival [13]. A post hoc analysis on data from 56 patients enrolled in a randomized controlled trial on PEEP setting strategies confirmed that ΔP_L and ΔP have comparable efficacy in predicting mortality [14▪▪]. In this study, although the majority of the respiratory system ΔP was accounted for by the lungs, a significant portion (roughly 33% on average) was secondary to the influence of the chest wall.

DRIVING PRESSURE DURING SPONTANEOUS BREATHING

Spontaneous breathing during ARDS may enhance lung aeration, prevent diaphragm atrophy, and improve hemodynamics [15,16]; however, inspiratory effort can lead to VILI because of high lung stress and strain, tidal recruitment in dependent lung regions and *pendelluft* phenomenon [17▪,18–20]. The use of partially assisted mechanical ventilation is frequent in the recovery phase of

ARDS, but very few data thoroughly described respiratory mechanics in spontaneously breathing patients with ARDS.

Notwithstanding that airway pressure during assisted mechanical ventilation is usually lower than during controlled mechanical ventilation, dynamic transpulmonary pressure (P_{Ldyn}), defined as the swing in transpulmonary pressure during inspiration and computed as the difference between airway and esophageal pressure, may reach very high values because of intense inspiratory effort [21].

However, being measured when flow is not zero, P_{Ldyn} reflects not only the elastic but also the resistive properties (because of airway resistance) of the respiratory system. In addition, airway resistance significantly varies with flow, making difficult to assess to what extent P_{Ldyn} reflects changes ΔP or ΔP_L [22].

Georgopoulos *et al.* reported the results of a study comparing ΔP during controlled and proportional assist ventilation in a mixed cohort of intubated patients [23▪▪], a ventilator mode that continuously measures C_{RS} and thus allows the calculation of ΔP. The authors observed that critically ill patients during spontaneous breathing controlled ΔP by sizing the V_T to individual respiratory system compliance. Thus, ΔP was similar during control and assisted mechanical ventilation and mostly kept below 15 cmH_2O, whereas V_T was not. Interestingly, the authors suggested ΔP as a possible target of feedback mechanisms aiming at limiting lung injury. Whether this is true in the specific subgroup of patients with ARDS needs confirmation.

Bellani *et al.* recently showed the feasibility of P_{plat} measurement (2-s inspiratory hold, aiming to obtain a period of no muscle activity) and reported the behavior of alveolar pressure both during controlled and assisted mechanical ventilation [22]. With the same PEEP applied, no difference was found in airway and lung P_{plat}, C_{RS}, C_L, and V_T between controlled and assisted ventilation at similar volumes and flow, indicating that both ΔP and ΔP_L are similar in the two conditions. The study was conducted in patients with mild severity (mean PaO_2/FiO_2 ratio of 224 mmHg, mean C_{RS} of 43 ml/cmHO). Given the feasibility of P_{plat} measurement during pressure support ventilation, further studies are warranted to investigate the behaviour of ΔP in spontaneously breathing patients with ARDS.

STRATEGIES TO LOWER DRIVING PRESSURE

Driving pressure may be the most useful ventilatory variable to stratify patients' severity and the risk of VILI at the beginning of ARDS. Moreover, it can be considered as simple and bedside tool to reliably assess the effectiveness of interventions and to monitor the course of the disease.

It seems physiologically reasonable to hypothesize that strategies to limit ΔP may provide a relevant clinical benefit, but no study has prospectively assessed whether systematic interventions titrated to ΔP reduction improve clinical outcome. Nevertheless, it must be noted that evidence concerning a safe level of ΔP to achieve when adjusting ventilator settings is lacking: currently, limiting ΔP to values equal or lower than 14 cmH_2O seems to be the wisest approach [1▪▪].

DRIVING PRESSURE LIMITING DURING CONTROLLED MECHANICAL VENTILATION

Different strategies can be used to limit ΔP during ARDS. As suggested by Amato, PEEP setting can significantly modify ΔP, as it affects the amount of aerated lung and hence C_{RS} [8▪▪]; however, this topic goes beyond the purposes of the present manuscript and will not be discussed further.

Prone position

Prone positioning has been convincingly shown to improve survival of patients with ARDS. Changes in both lung and chest wall mechanics contributing to a more uniform gas insufflation have been addressed as possible mechanism [24,25]. Cornejo *et al.* [26] showed that, when high PEEP is applied, prone position may reduce tidal hyperinflation, alveolar cyclic recruitment/derecruitment and slightly decrease ΔP, leading to the idea that changes in ΔP may contribute to the effects of prone position on survival.

Muscle paralysis

Muscle paralysis in the early phase of the disease has been shown to improve patients' outcome [27]. The mechanism hypothesized to explain this evidence is a lower transpulmonary pressure during muscle paralysis, along with improved patient–ventilator interaction, thanks to the avoidance of high-strain double cycled breaths or other dyssynchrony [28]. Whether this may be reflected by changes in ΔP or ΔP_L is unknown, but sedation and paralysis remain a crucial instrument to enhance efficient and rigorous protective and ultra-protective ventilation in the very early phase of the disease.

Increase CO_2 clearance

When low tidal volumes are applied, patients may be burdened by various degrees of hypercapnia and respiratory acidosis. Some simple and bedside available procedures leading to lower dead space can allow reducing V_T and ΔP in isocapnic conditions. Heated humidifiers, as compared to heat and moisture exchangers, decrease instrumental dead space and improve CO_2 clearance. Moran *et al.* conducted a crossover study showing that heated humidifiers allow to reduce V_T from 7.3 to 6.1 ml/kg PBW and P_{plat} from 25 to 21 cmH_2O without CO_2 changes [29]. Because PEEP was stable (average value 9 cmH_2O) over the entire course of the study, we may hypothesize that heated humidifiers may lead to a decrease in ΔP (i.e. from 16 to 12 cmH_2O) similar to P_{plat} reduction.

Some authors have suggested that a longer end-inspiratory pause enhances diffusion between inhaled V_T and resident alveolar gas, thus facilitating the transfer of CO_2 from alveoli toward the airways [30]. Accordingly, Aguirre *et al.* recently reported the results of a study on 13 patients with ARDS, demonstrating that a longer end-inspiratory pause (from 0.17 to 0.7 s) reduces dead space fraction and enhances CO_2 washout, finally allowing to lower V_T and ΔP (13.6 to 10.9 cmH_2O) with stable CO_2 and no development of auto-PEEP [31▪].

Ultra-protective ventilation with CO_2 removal

As previously highlighted, some patients may be at risk of overinflation even though V_T is 6 ml/kg PBW. Bein *et al.* showed that an ultra-protective ventilation strategy providing V_T as low as 3 ml/kg PBW and permitted by veno-venous extracorporeal CO_2 removal (ECCO2-R) can lower the driving pressure as compared to the standard 6 ml/kg PBW, but the clinical benefit (time to successful weaning) seemed to be limited to a post hoc subgroup of patients with PaO_2/FiO_2 ratio lower than 150 mmHg [32].

Nonetheless, to achieve such relevant V_T reduction, high blood flows (1.3 l/min) in the $ECCO_2$-R system were necessary and this aspect can limit the clinical application of the strategy.

Recently, the feasibility and safety of new devices allowing low-flow $ECCO_2$-R to enhance ultra-protective ventilation have been tested [33▪]. In a pilot study, 15 patients with moderate ARDS underwent V_T reduction to 4 ml/kg and low-flow $ECCO_2$-R was initiated when respiratory acidosis eventually developed. Mean $ECCO_2$-R flow of 420 ml allowed to significantly reduce V_T and ΔP, with no hypercapnia nor other side effects. A larger study with similar design is currently ongoing and will provide more definite results (NCT02282657).

Given that $ECCO_2$-R may not be available for all patients with ARDS, identifying patients that may most benefit from an ultra-protective ventilation strategy is a research priority.

Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation (ECMO) is increasingly being used as a rescue therapy for patients with most severe oxygenation impairment. Theoretically, given that ECMO allows oxygenation along with full extracorporeal CO_2 clearance, the ventilatory approach should aim at minimizing the risk of VILI without the need of providing any CO_2 washout.

However, ventilator settings during ECMO are still matter of debate and the management significantly varies across countries and institutions [34]. Despite observational studies indicating that V_T less than 4 ml/kg/PBW and P_{plat} less than 19–22 mmHg during ECMO are associated with improved survival, the latter is often hardly achievable if high PEEP is used [35]. Serpa Neto *et al.* recently conducted a pooled individual patient data analysis to investigate whether different ventilator settings during ECMO can affect patients' outcome. Initiation of ECMO was associated to lower V_T, P_{plat}, and improved C_{RS} but, again, lower ΔP during the treatment was the only ventilator variable associated to improved survival; also in patients undergoing ECMO, the effects of C_{RS}, V_T, and PEEP setting on mortality were fully mediated by changes in ΔP, finally suggesting a possible role of such parameter in this specific context too [36▪▪].

DRIVING PRESSURE LIMITING DURING ASSISTED MECHANICAL VENTILATION

Although sedation and paralysis is strongly recommended in the early phase of ARDS to minimize the progression of lung damage from a form of patient self-inflicted lung injury [37], assisted mechanical ventilation is often used in the recovery phase of the disease. Data concerning ΔP in spontaneously breathing patients with ARDS are lacking. Mauri *et al.* showed that inspiratory effort, P_{Ldyn} and V_T can be controlled through the use of extracorporeal $ECCO_2$-R while patients are recovering from ARDS [22]. Whether this can be associated to a lower ΔP is unknown and further clarifying studies are warranted.

CONCLUSION

Driving pressure allows identifying patients that are burdened by an increased risk of VILI and by a lower survival. Despite not demonstrated in clinical studies, targeting ventilatory interventions and V_T to achieve lower ΔP appears physiologically reasonable. It is wise to suggest that ΔP values higher than 14 cmH_2O should be avoided, but a really well tolerated individual threshold to achieve in patients with ARDS is yet to be identified.

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Conflicts of interest

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