Driving Pressure: What Is the Harm?*

KEY WORDS: acute respiratory distress syndrome; driving pressure; mechanical ventilation; ventilator-induced lung injury

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Mechanical ventilation is simultaneously a lifesaving intervention and the driver of ventilator-induced lung injury (VILI). Although we have devoted considerable effort to understand and mitigate VILI, thus far, restricting tidal volumes (Vts) is the only measure convincingly shown to be effective in doing so (1). This matters, as almost a quarter of ventilated ICU patients have acute respiratory distress syndrome (ARDS), for which mortality ranges between 35% and 46% (2). In the absence of targeted therapeutics, reducing the harm of ventilation may be our best means of improving outcome. In this issue of *Critical Care Medicine*, Urner et al (3) strengthen the case for limiting driving pressure (ΔP) as part of that effort.

Airway ΔP has been associated with VILI for 25 years (4). Yet, any causal interrelation remains a matter for debate (5). During controlled ventilation, ΔP is the tidal increase in static airway pressure applied across the integrated respiratory system (plateau pressure–positive end-expiratory pressure [P_{plat}–PEEP]) (4). In a given individual, this increase is proportional to Vt normalized to respiratory system compliance (Vt/Crs). The simplest mechanistic way to implicate higher ΔP in the generation of VILI is through its role in cyclic lung stretch. In the presence of lung inhomogeneity (e.g., ARDS), the cyclic stretch associated with a given Vt varies with the reduced resting volume of aerated "baby" lung. Used alone, Vts based on predicted body weight fail to account for that volume variation. By including a surrogate measure of resting aerated volume (Crs), ΔP attempts to do so, albeit imprecisely. Observational data support the superiority of ΔP over other measurable respiratory variables in predicting mortality during mechanical ventilation (6–9). Despite the alluring nature of the ΔP reduction concept, there are several important issues worth considering. First, the constituents of ΔP are coupled, both by mathematical derivation and by physiology. Modifying one of its determinants modifies the others—sometimes in unexpected ways. Establishing a causal link between ΔP and VILI is, therefore, difficult. As an example, imagine that as one increases a patient's Vt, this acts to recruit unaerated lung units and, thus, to minimize the expected rise in P_{plat}. The ΔP rises somewhat less than expected, and the patient has a better outcome. Now, which was causal—the reduction in the ΔP increment or the patient's underlying recruitability? Alternatively, if one keeps Vt unchanged but increases PEEP to some arbitrarily high pressure, that intervention may recruit unaerated lung and reduce the ΔP despite a higher absolute value of P_{plat}. Unfortunately, the patient has a bad outcome. Was the reduction in ΔP causal? Or rather, were the culprits higher values for PEEP and P_{plat}? Second, because transpulmonary ΔP acts on the lung, airway ΔP provides an incomplete measure of "lung" stress, as it fails to account for the contribution of chest wall elastance. This is of particular importance during spontaneous

***See also p. 861.**

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breathing or in the presence of a stiff chest wall. Finally, regardless of whether we choose airway ΔP or transpulmonary ΔP, the influence of other adjustable variables, such as flow rate, frequency, and power (the total energy delivered by the ventilator to the entire respiratory system per unit time), remain unaddressed. These issues, along with those particular to the design of observational studies, confound the literature. Thus, the link of ΔP to VILI causality remains elusive.

Urner et al (3) may have come closer to establishing causality. This was achieved by emulating a "target trial," that is, first designing a pragmatic randomized controlled trial (RCT) (the target trial) and then using observational data to emulate it. For other questions in mechanical ventilation, this approach has been reported to produce results similar to a contemporaneous RCT and thus is an attractive option when a conventional RCT is not feasible (10). The same method has been used by Urner et al (11) to study the effectiveness of extracorporeal membrane oxygenation in COVID-19 pneumonia. To test ΔP limitations, the authors used their institutional ICU registry, which contains records of almost 20,000 mechanically ventilated patients. From it, they entered all adult patients who received mechanical ventilation (invasive or noninvasive) within the first 24 hours of admission and for whom ventilation lasted more than 24 hours—12,865 patients in total. Their data included patients with and without acute respiratory failure of various etiologies. The baseline severity of illness was consistent with a general ICU population. Almost half of these patients breathed spontaneously. Given the real-world difficulties of measuring P_{plat} in spontaneously breathing patients, the authors chose to model a surrogate intervention: "dynamic" ΔP, defined as peak inspiratory pressure–PEEP. They supplemented data using this estimate of ΔP with data from a subgroup of patients who had available P_{plat} measurements. Regardless of the method used to calculate it, ΔP of the "intervention" group was limited to less than 15 cm H_2O daily, sustained for the duration of mechanical ventilation. While a safe limit for ΔP has not been established, this numerical value is consistent with the upper bound of safety derived from existing observational data (12). The control group received contemporaneous lung-protective ventilation, overcoming the issues of historical comparison found in earlier studies of ΔP limitation (6). Finally, the primary outcome was ventilator mortality to day 30. Liberation from ventilation or discharge from ICU were considered competing events for the primary outcome.

The results of this thoughtful analysis are intriguing. Urner et al (3) report an absolute reduction in the risk (ARR) of ventilator mortality of 1.9% (95% CI, 1.7–2.2%) when ΔP was kept less than 15 cm H_2O. This effect was evident, but less pronounced, when the analysis was restricted to those with static ΔP measurements. These are important results in themselves; however, secondary and sensitivity analyses provide reason to feel more confident about their implications. First, the relationship between ΔP limitation and mortality was dose dependent. For static ΔP, a strategy limiting ΔP to less than 25 cm H_2O had no effect on mortality, while limiting ΔP to less than 9 cm H_2O resulted in an ARR of 2.9% (95% CI, 1.2–4.9%). Second, starting later was less effective than starting earlier in the disease course. Limiting dynamic ΔP to less than 15 cm H_2O only after day 5 reduced the ARR from 1.9% to 0.9% (95% CI, 0.8–1.1%). Finally, the results were robust to "reversing" the treatment strategy (maintaining ΔP > 15 cm H_2O) and to applying that criterion to alternative outcomes (e.g., receipt of renal replacement therapy). Taken together, these data strongly suggest a link between limiting ΔP during mechanical ventilation and a reduction in mortality.

But are they sufficient? It may be wise to be cautious. Despite the strengths of the study by Urner et al (3) and the technical skill with which the authors have conducted it, it falls short of the RCT "gold standard." The "target trial" emulation method has important limitations, such as the effects of residual confounding and the influence of missing or misclassified data. The authors correctly argue that a RCT testing the same hypothesis would need to be large and larger than any conducted in this area before. This will present challenges with feasibility, but given the number of patients ventilated globally, a pragmatic trial of limiting ΔP should be feasible, particularly in the setting of the level of international collaboration currently seen in many critical care trials.

While an RCT dedicated specifically toward ΔP and outcome has not yet been conducted, several large trials which indirectly address the question have done so. The Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) used a complex "open-lung" strategy to test the hypothesis that improving lung

aeration improves survival (13). Using this strategy, the authors separated ΔP between the control and intervention groups by 1.5 cm H_2O (13.5 vs 11.7). Unexpectedly, 28-day mortality was higher in the "intervention" group (hazard ratio, 1.20; 95% CI, 1.01–1.42). Similarly, the pRotective vEntilation with veno-venouS lung assisT in respiratory failure (REST) trial of extracorporeal carbon dioxide removal for acute hypoxemic respiratory failure separated ΔP between the control and intervention groups by up to 2.8 cm H_2O (14). Again, mortality was numerically higher in the "intervention" group (90-d mortality risk ratio, 1.05; 95% CI, 0.83–1.33). A more recent secondary analysis of the trial goes further, finding that the mortality benefit of the intervention did not vary substantially with reduction in ΔP (15). Each of these studies manipulated a different determinant of ΔP; in ART—respiratory system compliance and in REST—Vt. If ΔP is merely an intermediate mediator of VILI and distant in the causal chain or simply a convenient monitor of those factors responsible (a possibility not excluded by Urner et al [3]), then manipulating its interlinked components may have unforeseen consequences. Such consequences are not modeled in a trial emulation. Furthermore, a target trial specifies the intervention (ΔP < 15 cm H_2O) without providing an indication of how it is achieved. Put more simply, it is not just what you do that matters but also how that you do it. This quandary is not unique. There is a long history of similar situations in critical care, where attempts to manipulate variables with equally strong associations to healthy status resulted in unanticipated harm, from anemia to oxygen delivery.

Urner et al (3) make an important contribution. Their results increase our confidence that targeting ΔP might be an effective means of reducing mortality during mechanical ventilation. However, these data do not conclusively confirm that ΔP is causally linked to VILI. Instead, this newest evidence indicates the need for well-designed and conducted RCTs capable of resolving the central question of whether limiting ΔP improves outcome.

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Predictors of Noninvasive Ventilation Failure in the Postextubation Period: What Else?*

KEY WORDS: extubation failure; high-risk extubation; noninvasive ventilation; positive pressure ventilation; predictors of noninvasive ventilation failure; weaning

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When the critical care practitioners have to extubate a critically ill patient from invasive mechanical ventilation they have to evaluate if the patient achieved the usually used clinical criteria to determine the readiness for spontaneous breathing trial (SBT): improvement of the cause of the acute respiratory failure, Pao_2/Fio_2 greater than or equal to 150 or Spo_2 greater than or equal to 90% on Fio_2 less than or equal to 40% with positive expiratory-pressure less than or equal to 5 cmH_2o, arterial pH greater than 7.25, hemodynamic stability (no or low dose of vasopressors) and ability to initiate an inspiratory effort. Additional criteria of adequate mental status (awake and alert or easily arousable), core temperature less than 38°C, hemoglobin level above 7 g/dL), no new infiltrate on chest radiograph and no current bronchospasm can be added to assure a more accurate and comprehensive clinical evaluation (1).

After this assessment, an SBT is performed, and if the patient successfully passes the test the critical care practitioner should evaluate the safety for extubation. This requires an evaluation of the volume of respiratory secretion, airway patency, and protection (sufficient cough and expiratory force to expectorate with an adequate level of consciousness to avoid aspiration). A study that evaluated the peak expiratory flow rate (PEF), sputum volume, and neurologic function showed that if PEF less than 60 L/min, sputum volume greater than 2.5 mL/hr, and the patient was not capable to follow commands, the incidence of extubation failure was 100% compared with 3% when none of these risk factors were present (2).

Then, the patient should be assessed for the risk of postextubation stridor, which occurs in 10% of the patients read for extubation, but is associated with increased rates of reintubation, prolonged duration of mechanical ventilation, and longer ICU length of stay (3). The critical care practitioner also has to check if the patient has any potential difficulty with reintubation, should extubation

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