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ABOUT COVER

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MINIREVIEWS

Driving pressure in mechanical ventilation: A review

Syeda Farheen Zaidi, Asim Shaikh, Daniyal Aziz Khan, Salim Surani, Iqbal Ratnani

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Abstract

Driving pressure (ΔP) is a core therapeutic component of mechanical ventilation (MV). Varying levels of ΔP have been employed during MV depending on the type of underlying pathology and severity of injury. However, ΔP levels have also been shown to closely impact hard endpoints such as mortality. Considering this, conducting an in-depth review of ΔP as a unique, outcome-impacting therapeutic modality is extremely important. There is a need to understand the subtleties involved in making sure ΔP levels are optimized to enhance outcomes and minimize harm. We performed this narrative review to further explore the various uses of ΔP, the different parameters that can affect its use, and how outcomes vary in different patient populations at different pressure levels. To better utilize ΔP in MV-requiring patients, additional large-scale clinical studies are needed.

Key Words: Driving pressure; Acute respiratory distress syndrome; Mortality; Positive end-expiratory pressure; Ventilator induced lung injury; Mechanical ventilation

Core Tip: Driving pressures (ΔP) of < 15 have demonstrated the greatest benefit in mortality. It is most utilized in patients with acute respiratory distress syndrome (ARDS). Some large-scale randomized controlled trials are currently underway; their results will dictate the outcomes of certain ΔPs under specialized conditions, such as the feasibility of reducing ΔP in ARDS patients on mechanical ventilation and the impact of lateral positioning on ΔP. It is clear, however, that careful implementation of ΔPs can greatly improve outcomes.

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INTRODUCTION

Driving pressure (ΔP) is a fundamental element in mechanical ventilation. Its primary function is to overcome the elastic forces of the pulmonary system. It is derived from the difference between end-inspiratory airway pressure, commonly known as the plateau pressure (Pplat), and positive end-expiratory pressure (PEEP) in the absence of spontaneous respiration[1-4].

ΔP is derived from the ventilator and serves as a function of respiratory compliance and tidal volume. It reflects the pressure difference within a singular breath and is one of the major parameters implicated in lung stress[5,6]. Recent studies have shown a plausible association between ΔP and improved survival in patients with acute respiratory distress syndrome (ARDS)[5,7-13]. Even though it is commonly used across critical care centers around the globe, it is a measure that requires further introspection to harness its predictive potential and guide safe and effective ventilation.

This review article discusses the dynamics of mechanical ventilation and explores the role of ΔP, its significance in recent studies, and the resulting implications for future research.

PHYSIOLOGY AND MECHANICS OF MECHANICAL VENTILATION

Mechanical ventilation allows gas exchange and attenuates increased work of breathing in the setting of an acute compromise of the respiratory system. The mechanics are expressed through indices such as pressure, flow, volume, resistance, work of breathing, and compliance, which directly influence lung volumes, functional residual capacity, and the resulting gas exchange[5].

Physiologically, the respiratory circuit works as a negative pressure system. On inspiration, the diaphragm is pushed down, and negative pleural cavity pressure is generated. A net negative pressure in the airway serves as a suction for air to be brought into the lungs. The negative pressure then, in turn, decreases the right atrial pressure and generates a similar suction effect in the inferior vena cava, which results in an increase in venous return[14].

During mechanical ventilation, however, this physiology is altered, and a positive pressure is transmitted into the pulmonary system instead. This leads to a more positive pressure in the pleural space and less of that suction effect. This positive pressure is also exerted on the right atrium, which leads to a decrease in venous return and preload. The net impact is a reduced cardiac output due to the underfilling of blood in the left heart and low mean arterial pressures[15]. An understanding of the effects of artificial ventilation is important to guide management in patients and adjust for the consequences.

The baby lung concept was coined by Gattinoni and Pesenti[16] after they observed computed tomography scans of patients with ARDS or acute lung injury. They noticed that the total aerated lung tissue of these patients held dimensions of 300-550 g, similar to a 5-6-year-old child. They proposed that the ARDS lung is not stiff but, in fact, functionally small-suggesting that the elasticity of the lung is most likely intact and that the lung tissue may change dimensions after recruitment maneuvers such as prone positioning. They highlighted that gentle lung treatment should thus be employed to avoid baro-volutrauma inflicted by standard aggressive resuscitative strategies. This theory has gained traction as further research on ARDS has supported their findings, and the discovery and application of ΔP in research has improved outcomes[17]. In general, a tailored approach to ventilation is required to match a patient's variable physiology to reduce the chances of ventilator-induced lung injury (VILI).

FACTORS THAT INFLUENCE THE MECHANICS OF ARTIFICIAL VENTILATION

Impedance

The forces that impede ventilation include non-elastic or respiratory system resistance, which occurs when gas flows within the airway circuit, and elastic resistance, which occurs in the absence of gas flow in the circuit[18]. Examples of non-elastic resistance include frictional resistance to gas flow, viscoelastic resistance from the deformation of thoracic tissues, and finally, the inertia of gas flow and tissue movement[18]. While small levels of impedance do not always mean

underventilation of lung tissues, higher levels of impedance require higher ΔPs for effective ventilation. These forms of resistance can be reflected in the equation: *(*Resistance R = Δ pressure/flow).

The elastic resistance comprises of resistance exerted by the chest wall and lung tissue, along with resistance exerted by the surface forces at the alveolar gas-liquid interface. The elastic resistance can be used to derive total compliance of the lung and the chest wall[18]. These forms of resistance can be represented by the following equations: (Compliance Crs = Δ volume/Δ pressure), [Elastance (EL) ELrs = Δ pressure/Δ volume = 1/C].

As a rule, high levels of compliance, and therefore lower levels of EL, allow for less effective mechanical ventilation at lower ΔPs. Hence, in certain conditions that alter these mechanics, such as in emphysema, which leads to higher compliance, increased levels of ΔP are required to maintain adequate levels of ventilation.

PRESSURE

Airway pressure

Airway pressure is equal to alveolar pressure in the resting state and depicts the pressure generated to overcome the retractive elastic forces of the pulmonary system. It is reflected in the following equation[19,20]; (airway pressure = flow x resistance + alveolar pressure).

Airway pressure dictates the ΔPs required for adequate ventilation in all patients. Higher alveolar pressures and general airway resistance require increasing levels of ΔP to maintain effective ventilation.

Pplat

Pplat is the pressure exerted by the ventilator into the alveoli and small airways of the lung. It is calculated during an inspiratory pause of 0.5-1 s on the ventilator when the respiratory muscles are relaxed. This pressure approximates the mean peak alveolar pressure[21,22]. As noted previously, resting high Pplats are incorporated in ΔP calculations in order to identify requirements for overcoming inside pressures.

Transpulmonary pressure

Transpulmonary pressure (P_{TP}) is the distending pressure of the lungs and is derived by calculating the difference between the pressure within the alveoli (P_{ALV}) and the pleural pressure (P_{PL})[23]. The transpulmonary pressure is described by the following formula: ($P_{TP} = P_{ALV} - P_{PL}$).

ΔP

ΔP is derived from the difference between Pplat and PEEP. It is essentially the pressure required to open the alveolar sacs. Since static lung compliance (Cstat) is derived from the formula; Tidal volume/(Pplat-PEEP), ΔP is derived as an inverse function of respiratory system compliance (C_{rs}). The higher the ΔP, the lower the compliance of the lung and, therefore, an increased risk of volutrauma. Henceforth, ΔP is the foundational pillar of mechanical ventilation. Adequate ΔP levels are needed for effective air delivery to overcome resistances, high inner pressures, and losses during ventilation. It is described by the following equations[24]: (ΔP = Pplat - PEEP), ($\Delta P = VT/C_{rs}$).

Transpulmonary ΔP

Transpulmonary ΔP (ΔP_{pL}) can be defined as the difference between the P_{TP} at end inspiration and end-expiration.

Peak pressure

Peak pressure is the maximum recorded pressure at the end of inspiration in the presence of airflow. Peak pressure is dependent on tidal volume, respiratory rate, and airflow[14,20].

Intrinsic PEEP

Intrinsic peak expiratory pressure reflects the pressure exerted by the residual volume in the lung due to incomplete exhalation. It can be calculated by doing an expiratory pause and measuring the end-expiratory pressure[14].

Stress

Lung stress refers to the pressure required to distend the lung against the counterforce exerted by the chest wall. Stress is depicted best by P_{TP}, which is the difference between airway pressure (Paw) and P_{PL}. Its formula is represented by ($Paw-P_{PL}$).

Despite its high predictability, P_{TP} is not frequently used due to the difficulty of calculation, and Pplat is thus used as an alternative. Pplat is reflective of alveolar pressure when the airflow is zero and is calculated during an inspiratory pause on the ventilator when the respiratory muscles are relaxed.

Strain

Lung strain is directly related to lung stress and refers to the change in lung volume when compared to its volume during regular respiration[20,23,25].

MODIFIABLE INPUTS IN ARTIFICIAL MECHANICAL VENTILATION

Tidal volume

Tidal volume is the amount of air exchanged during ventilation at rest and is matched by ideal body weight or approximations based on the patient's disposition[14]. Tidal volume follows a proportional relationship with ΔP in mechanical ventilation. Higher tidal volumes increase ΔPs. This can be modified as needed.

PEEP

PEEP or extrinsic PEEP is the end-expiration pressure that is delivered by mechanical ventilation to prevent the lung from collapsing. It is important to maintain the patency of the small airways and alveoli. This, in turn, increases lymphatic flow and allows adequate drainage of the lung. Therefore, lower levels of PEEP increase ΔPs.

Respiratory rate

The rate of ventilation is set to achieve target levels of carbon dioxide according to the patient's metabolic demands[14]. Respiratory rate is a component of mechanical power (MP) along with ΔP. These levels can be changed depending on ventilation requirements and desired MP metrics.

MEASURES OF PATIENT-MACHINE INTERACTION

Mechanical energy

Mechanical energy (EnergyL) refers to various forms of energy transferred after each ventilatory cycle and can be derived simply through Pplat (ΔPL) and the EL of the lung. It is described in the following formula(s): (EnergyL = ΔPL 2/EL), [(EnergyL = ΔV2 × [(0.5 × ERS + RR × (1 + I:E)/60 × I:E × Raw) + ΔV × PEEP)].

MP and intensity

MP refers to the EnergyL multiplied by the rate of respiration, thus reflecting the EnergyL transferred per minute from artificial ventilation. This value captures both static and dynamic metrics that influence respiration[26]. MP has recently emerged as a novel and promising predictor of VILI. While its incorporation clinically is yet to be widened, it has shown promise. Maintaining lower rates of MP by considering the dynamic metrics it incorporates, can reduce rates of VILI. The formula of MP is reflected as [*MP = (EnergyL x RR) or RR W=RR ∫0 VT PawdV∫*]

CLINICAL RELEVANCE OF ΔP

In recent years, the understanding behind VILI has rapidly expanded from a limited perspective of pressures, volumes, and tidal cycles to an understanding of forces and their interplay in periods of stress and strain while being subjected to different forms of energy and power. The value of ΔP has recently gained traction in research and practice due to key findings demonstrating the impact of high ΔPs, resulting in low compliance and increased risk of volutrauma. Ultimately lead to higher morbidity and mortality in patients requiring artificial ventilation-particularly in cases of ARDS.

A meta-analysis by Amato *et al*[3] analyzed 9 randomized controlled trials and demonstrated that in intensive care settings, ARDS patients with elevated ΔPs of 15 cm H_2O were positively associated with higher mortality (relative risk, 1.41; 95%CI: 1.31 to 1.51; $P < 0.001$), (relative risk, 1.36; 95%CI: 1.17 to 1.58; $P < 0.001$), after every 1 standard increment in ΔP (approximately 7 cm of water). This result was despite the protective range of tidal volumes and Pplat[3]. A ΔP less than 15 cm H_2O was considered to be a safe threshold to guide ventilation in ARDS patients and decrease mortality[3]. This study, despite its limitations, provided a significant understanding of the delicate role ΔPs can play in the management of ARDS and the intricate and precise difference the slightest of modifications can make.

In addition, the large observational cohort study to understand the global impact of Severe Acute Respiratory failure (LUNG-SAFE), a multicenter, international study, was conducted to identify the incidence of ARDS in intensive care units but also to collect information about the associated ventilatory management, therapies, and outcomes. The multivariate analyses concluded that high peak pressures, higher Pplats, high ΔPs of > 14 cm H_2O, and low PEEP were associated with increased mortality in these patients[27].

This notion gained additional strength when Bellani *et al*[28], in their retrospective study, also demonstrated that a higher ΔP was associated with higher mortality rates. Chiumello *et al*[2] revealed that ARDS patients with higher than threshold values of ΔP experienced lung stress and thus were likely to experience more ventilator-associated lung injury due to cyclic stretch. It can, therefore, be inferred that the ΔP reflects the stress on the lungs and that outputs like tidal volumes should be adjusted for ΔP instead of traditional measures. Similarly, PEEP can be adjusted to accommodate the loss of airway recruitment, increased levels of stress and strain, and the resulting increase in ΔP. A higher PEEP will improve lung compliance and attenuate the high ΔPs resulting from lung inhomogeneity[29,30].

Villar *et al*[31] provided evidence that ΔP was related to an increase in hospital mortality despite optimized protective ventilation. In addition, Urner *et al*[32] assessed the dose-effect relationship between ΔP and survival. A hazard ratio of 1.064 (95%CI 1.057-1.071) was seen with a daily increment of ΔP. A higher mortality was noted with ΔP levels of ≥ 15 cm H_2O, even if present for brief period. Furthermore, a higher ΔP level had a greater increase in mortality when compared

to PaO_2/FiO_2 or other metrics of oxygenation.

While it has emerged as a promising metric to help attenuate events of VILI, despite reliable estimation of lung pressures, ΔP alone may not provide an accurate measure of risk. The process of VILI occurs due to a complex interplay of various forces, therefore multiple parameters need to be accounted for and addressed when managing mechanical ventilation in these cases.

MONITORING, MEASUREMENT, AND PATIENT CHARACTERISTICS

ΔP is measured in two ways. Firstly, in the setting of an absence of spontaneous breathing, an end-inspiratory hold of a few seconds on the ventilator provides the value of Pplat. The ΔP can be derived from the following formula (Pplat-PEEP). This method can be vulnerable to oversimplification and bias when auto-PEEP is significant and not accounted for. It can also be erroneous when clinical leaks such as bronchopleural fistulas or micro leaks are found in the apparatus or tubing. These errors can result in second-by-second variability in Pplat values. A way to counter this discrepancy is to shift the ventilator to volume control mode and set a shorter inspiratory pause of 0.3 s. This method will provide consistent measures of Pplat and thus more reliability due to shorter occlusion periods[33].

Foti *et al*[34] described the method of calculating ΔP in static conditions with pressure support ventilation. The derivation of Pplat is performed after an end-inspiratory hold and respiratory muscle relaxation [when the pressure generated by the ventilator (Paw) reaches a plateau] This method was proven by Akoumianaki *et al*[35] to overestimate Pplat and ΔP due to confounding by expiratory muscle activity. Another potential problem that distorts an accurate read of the Pplat is reverse triggering, wherein a patient initiates inspiratory effort during the middle or end of a passive inspiration by the ventilator. This is a form of ventilator desynchrony that tends to occur when a patient is weaning off sedation or paralysis. This results in an underestimation of Pplat due to a misleading drop in end-inspiratory pressures [36].

Therefore, in the case of spontaneous breathing, the derivation of ΔP becomes slightly more complex, as the patient component of respiratory effort needs to be accounted for, which is essentially driving the breath. Therefore, the pressure applied by the ventilator (Pplat-PEEP) needs to be added to the pressure generated by the respiratory muscles; *i.e.*, P_{PL}. The P_{PL} can be accurately estimated through esophageal manometry, and this dynamic measurement is called the PL swing. The swing describes the ΔP for insufflation of the lung and generation of flow representing the overall change in P_{PL}[37]. Therefore, during spontaneous breathing, the formula of ΔP changes to the following: $\Delta P = (Pplat\text{-}PEEP + \Delta P_{PL})$.

Another important value Bertoni *et al*[38] investigated was the ΔPocc (occluded inspiratory airway pressure), also known as the Pes swing. This value emerged from performing an expiratory hold to ascertain the patient's inspiratory effort. The deflection depicts the change in P_{PL}. This was described as dynamic P_{PL}. The equation to describe dynamic P_{PL} is: *Predicted dynamic* $P_{PL} = [\Delta P_{Ldyn} - (Ppeak - PEEP) - 0.66 \times \Delta Pocc]$. In addition to this, Telias *et al*[39] also showed the value of the airway occlusion pressure (P0.1) metric that is measured in the first 100 ms. of an occlusion. This metric was used to accurately detect inspiratory effort and low ventilatory drive. P0.1 can also be used to ascertain high values of dynamic.

ΔP IN SPECIAL POPULATIONS

ARDS

In ARDS, the lung becomes less compliant, resulting in a reduced proportion of recruitable tissue that can be ventilated. This was best illustrated by the previously described baby lung concept[16]. These alterations thus require modulation of ventilatory techniques to account for the loss of lung volume, such as adjusting tidal volume with compliance and increasing PEEP to target ΔP[3]. As discussed earlier, many studies have described the role of ΔP in patients with ARDS. The strong association of cyclical stretch and lung stress correlates with ΔP and overall survival in ARDS.

Blondonnet *et al*[40] analyzed ΔP at baseline and at 24 h in patients who had developed ARDS. The analysis showed that both baseline ΔP and respiratory rate were significantly lower. ΔP greater than 16.5 cm H_2O was predictive for ARDS development and vice versa. Similarly, Haudebourg *et al*[11] demonstrated that ΔP-targeted ventilation in patients with moderate to severe ARDS improved ventilatory parameters such as increased tidal volumes, lower MP requirement, and reduced respiratory rate. In addition, Guérin *et al*[7], in their study, showed that ΔP was more strongly associated with survival as compared to PEEP and tidal volume in ARDS patients. While many studies have highlighted the role of ΔP and its influence on outcomes, some studies suggest otherwise.

One such study by Romano *et al*[41] compared limiting ΔP with standard lung protective measures during ventilation of patients with ARDS. The tidal volume was set according to ideal weight; 4-8 mL/kg and a ΔP of 10 or the lowest possible was applied. The comparison group was ventilated according to the ARDSNet protocol with adjustments made in tidal volume based on Pplat. It was seen that both the ΔP and tidal volumes were lower in the ΔP-limited group as opposed to the conventional group, although there was no effect on outcomes.

Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation (ECMO), an external circuit to directly oxygenate the blood and remove carbon dioxide, was unveiled in the 1970s, but its use took off in more recent years, increasing to a whopping 433% since 2006 [42]. ECMO is used to rest the lungs and decrease stress, strain, and intensity experienced in mechanical ventilation. It provides cardiac, respiratory, or cardiorespiratory support when needed. Ultra-low tidal volumes are employed, and

various strategies are used to achieve this. Current guidelines for mechanical ventilation with ECMO, target Pplat and tidal volumes corrected for ideal body weight[43].

A study by Gupta *et al*[44] analyzed ΔPs pre- and post-ECMO initiation to compare how high and low ΔPs influence mortality and outcomes. In this study, 46% of patients had increased ΔPs and higher drops in PEEP post-ECMO initiation. The study also showed a significantly longer length of ECMO stay in patients, perhaps due to poor parameters influencing clinician decision of weaning. High ΔP in ECMO was seen as a strong predictor of 30-d mortality in both adjusted and unadjusted analyses of patients receiving ECMO in both groups.

Magunia *et al*[45] showed in their study of patients receiving VV-ECMO that survivors had increased compliance levels and lower ΔPs as compared to non-survivors. Similarly, Chiu *et al*, in their study of patients with severe ARDS on ECMO, showed that the cut-off point between survivors and non-survivors was a 33% change in ΔP within the first 12 h with a sensitivity of 78% and a specificity of 67.9%[46].

In the study by Del Sorbo *et al*[47], the effects of changing ΔP were correlated with various variables. A linear relationship was demonstrated between the change in ΔP and the concentration of certain inflammatory mediators that correlate with VILI in lung epithelial cells. This finding suggests a strong predictive potential for VILI if ΔP is utilized adequately in these patients.

Surgical

In the surgical setting, there is a high likelihood of pulmonary complications, particularly in thoracic surgery, due to direct injury of lung tissues and open ventilation of one lung. This results in a heightened immune response and increased pulmonary vascular permeability, resulting in ARDS[48].

Blank *et al*[49] analyzed the ΔP and tidal volumes of patients undergoing thoracic surgery with two or one-lung ventilation and found that ΔP was a risk factor for overall postoperative morbidity with an odds ratio of 1.034 (97.5%CI. 1.001 to 1.068). In a meta-analysis of surgical patients, Neto and colleagues demonstrated a positive correlation between postoperative respiratory complications in patients with higher ΔPs with an odds ratio of 1.16 for each 1 cm H_2O increase in ΔP. No significant associations were found with tidal volume, and PEEP was only influential if it altered the ΔP[50].

In a cohort study conducted by Mathis *et al*[51] of cardiac patients undergoing surgery, modified ΔP was independently associated with decreased pulmonary complications. However, it was not clear whether active control of ΔP would result in improved outcomes, and the method of controlling or reducing ΔP was not particularly defined in their study.

Park *et al*[52] randomized patients who were receiving elective thoracic surgery into two ventilatory groups. One group was ventilated with standard measures of low tidal volumes, a peep of 5 cm H_2O, and tailored maneuvers to increase recruitment were utilized as needed. Low tidal volumes were used in the second group, but PEEP was titrated according to the desired ΔP. Postoperative pulmonary complications were higher in the first conventional group (12.2%) as compared to the second group, where ΔP was titrated (5.5%). The incidence of ARDS was also elevated in the first group (5 patients) as opposed to the second group (0 patients). Despite the impressive findings, there was no impact on the development of ARDS by day 7, nor was there any decrease in the length of intensive care unit (ICU) and hospital stay.

COPD

In the setting of chronic obstructive pulmonary disease, there is increased air trapping, obstruction, and elevated airway resistance. This leads to an increase in end-expiratory lung volume and an increase in end-expiratory alveolar pressure-also referred to as intrinsic peep. It is thus necessary to utilize an end-expiratory and inspiratory hold to accurately generate compliance and therefore ΔP[53]. Although specific studies on COPD patients and the role of ΔP in their ventilation have not been captured, COPD patients require monitoring to ensure the emptying of lung air and thus, PEEP is primarily adjusted.

Obesity

Obese patients typically have higher chest wall EL, low or more negative P_{TPs}, and lower compliance. Due to the variability of these values, a true reflection of ΔP cannot be obtained accurately. In obese patients, transpulmonary ΔP is more reliable, but more studies are required to better explain these assumptions[54]. De Jong *et al*[55] studied the relationship between ΔP during the first day of ventilation and 90-d mortality in 100 obese patients and 262 non-obese patients with ARDS but found no association between ΔP and mortality in obese patients. A limitation of the study was the reliance on body mass index as a measure of obesity and body fat percentage was not accounted for.

Pregnancy

In pregnancy, the physiology of the respiratory symptom is altered. Due to the chemical effects of progesterone and prostaglandins E1 and E2, bronchodilation occurs. Prostaglandin F2alpha, however, can increase airway resistance and constrict bronchial smooth muscles. In addition, due to uterine distension, the diaphragm is elevated, and there is an increase in end-expiratory abdominal pressure (Pga). The P_{PL} also increases, leading to a reduction in expiratory residual volume (ERV) and functional residual capacity (FRC) due to early closure of small airways. The chest height also becomes shorter and ERV is 8%-40% lower during the second half of pregnancy. The tidal volume and occlusion pressure also increase, reflecting a need for adjustment for ventilation[56,57].

Respiratory failure in pregnancy is rare, occurring in 1 in 10000 pregnancies, but its incidence has increased, particularly since coronavirus disease 2019 (COVID-19)[58]. A study by Vasquez *et al*[59] showed that respiratory mechanics in pregnant females remained similar to the general population that required ventilation in cases of COVID. In a study by

Lapinsky *et al*[60], they conducted a retrospective analysis of the impact of COVID-19 on mechanical ventilation parameters. In the case of ΔPs, survivors had an average of < 14 cm H_2O, and non-survivors had higher ΔPs. Post-delivery, there was an increase in the PaO_2/FiO_2 ratio, but there was no change in static compliance or ΔP.

Pediatric

The first pediatric study to assess ΔP in mechanically ventilated children was conducted by Schelven *et al*[13] In their study, they demonstrated higher disease severity, MV indication, and an increase in extubation time in patients with higher ΔP[1]. Similarly, a retrospective study by Rauf *et al*[9] assessed the effects of ΔP on morbidity and mortality in children admitted to the ICU with ARDS. The study divided the children into two groups; one with ΔP of 15 cm H_2O in the first hour and the other with lower than 15 cm H_2O ΔP. It was seen that children with lower pressures had significantly lower morbidity in ARDS. A study by Yehya *et al*[61], however, suggested that ΔP in children with ARDS was not an independent predictor of mortality. It is worth noting that ΔP was not accurately defined in either of these studies.

Elderly

Aging can result in an alteration of lung physiology through increased pro-inflammatory and fibrotic factors. Decreased chest wall compliance and higher levels of air trapping are noted due to the loss of lung tissue, which ultimately leads to a reduction in FEV1[62]. No study has specifically explored the effects of aging on ΔP. Theoretically, it is assumed that it would increase ΔP due to the change in compliance. It is clear that elderly patients are far more susceptible to higher morbidity and mortality in the ICU setting, and several studies have reported age as a strong predictor for mortality[63-66].

Heart failure

Cardiac failure due to structural and functional causes frequently results in pulmonary edema, which requires mechanical ventilation strategies. In a fluid-filled lung, the lung's compliance dramatically decreases, and the resistive forces increase. The lung behaves in a similar way to ARDS due to the pulmonary edema and, therefore, holds the same pathological changes in mechanics.

In an observational study by Yang *et al*[67], they analyzed 632 patients with heart failure who required invasive ventilation. It was found that higher ΔPs above a threshold of 14.27 cm H_2O were found to be independently associated with increased in-hospital mortality if patients were ventilated over 48 h. With each increment of 1 cm H_2O of ΔP, an increased odds ratio of 1.12 in the risk of in-hospital mortality was observed. In contrast, Schmid *et al*'s study showed that there was no association with mortality in non-ARDS patients, including patients with heart failure and other cardiac-related diseases[10]. A summary of the cumulative findings of ΔP in special populations is shown in Table 1.

CLINICAL OUTCOMES

A cohort study by Goodwin *et al*[68] examined electronic health records to ascertain the importance of ΔP and EL in influencing clinical outcomes. The study assessed various factors in 2334 homogenous patients with respiratory failure in the ICU. After adjustment for covariates, exposure to ΔPs > 15 cm H_2O was associated with a 19% increased risk (1.19; CI 1.07-1.33) of mortality and 1.5 fewer ventilator-free days as compared to controls. Increased respiratory EL of > 2 cm H_2O/mL/kg was also associated with a 13% increase in the risk of mortality without any impact on the length of stay or ventilatory-free days. This study established a time-weighted averaging method to derive exposure of ΔP and other metrics to give a consistent reading of ΔP and its resulting influence[2].

ΔP and EL have been shown by numerous studies as predictors of reduced lung function, increased stress, and a high likelihood of VILI. Employing LUNG-SAFE ventilation strategies has expanded from lowering tidal volume to acceptable thresholds of plateau ΔPs and reducing ventilation frequency. Currently, values of Pplat of 30 cm H_2O and ΔP of 15 cm H_2O are considered the upper limit. Intervention is thus necessary to tailor ventilatory care[69-71].

FUTURE DIRECTIONS AND LATEST RESEARCH

Many studies have provided significant insight into the relevance of ΔP as a detrimental factor in guiding ventilation. These studies have demonstrated this by showcasing high numbers of adverse events in the setting of elevated ΔP. It is worth noting that these studies are not without limitations, with many of them lacking causality. Therefore, there is a need for more comparative analyses to better predict the validity of ΔP when compared to other parameters such as PEEP, EL, tidal volume, MP, *etc.* A standardized method of quantifying ΔP is also crucial to ensure accuracy, and a protocol should be introduced for clinicians to follow if they plan to conduct further research on the impact of ΔP. The adjunct of additional modalities, such as Electrical Impedance Tomography (EIT) and Ultrasound, will further improve validity and give valuable insight[27]. ΔP in ECMO should also be utilized and studied to extract valuable findings.

It is common in studies to derive ΔPs during passive ventilation, but efforts should be made to explore ΔPs in the presence of spontaneous breathing. This will deliver additional comparative data and assess whether there are any shifts in ΔP while revealing additional metrics that may directly or indirectly influence results. The newer generation of ventilators should also be introduced when feasible-to guide clinicians in accounting for all the dynamic and static forces

Table 1 Findings from clinical studies regarding driving pressure

Population	Ref.	Study design	Sample	Findings
ARDS	Blondonnet *et al*[40]	Prospective cohort; secondary analysis	221 patients with at least 1 risk factor for ARDS	15% developed ARDS within 7 d who had higher baseline ΔP
ARDS	Guerin *et al*[7]	2 randomized controlled trials	787 patients	DP was more strongly associated with survival as compared to PEEP and tidal volume in ARDS patients
		Secondary analysis		PEEP and Tidal volume were not associated with death in any model
ARDS	Romano *et al* [41]	Pilot randomized, controlled, nonblinded trial	31 patients with ARDS on invasive mechanical ventilation with a driving pressure of ≥ 13 cm H_2O	DP and tidal volumes were lower in the driving pressure-limited group as opposed to the conventional group, although there was no effect on outcomes
ARDS	Chiumello *et al*[2]	Prospective cohort	150 patients	At ICU admission, non-surviving patients had a higher arterial carbon dioxide compared to survivors; The transpulmonary driving pressure was significantly related to the airway DP; The transpulmonary driving pressure was significantly related to lung stress
ARDS	Amato *et al*[3]	Meta-analysis of 9 RCTs	3562 patients in the ICU	ARDS patients with elevated DP of 15cm H_2O were positively associated with higher mortality; A DP of less than 15 cm H_2O was a safe threshold to guide ventilation in ARDS patients and decrease mortality
ARDS	Bellani *et al* [27]	Prospective cohort	459 ICUs; 12906 patients	High peak pressures, higher plateau pressures, high driving pressures of > 14 cm H_2O, and low peep were associated with increased mortality; There was a direct relationship between both plateau and DP and mortality
ARDS	Bellani *et al* [29]	Retrospective cohort study	154 patients	DP was higher, compliance was lower and peak pressure was similar, in non-survivors versus survivors; Lower respiratory system compliance and higher driving pressure were each independently associated with an increased risk of death
ARDS	Urner *et al*[32]	Registry-based cohort study	9 ICUs; 12865 patients requiring > 24 h of mechanical ventilation	Mortality was 18.1% with DP < 15 cm H_2O compared with 20.1% under usual care
ARDS	Haudebourg *et al*[11]	Prospective cohort	51 adult patients	The change from PBW to ΔP-guided ventilation was thus accompanied by an overall increase in tidal volume from 6.1 mL/kg PBW to 7.7 mL/kg PBW (6.2-8.7), while the respiratory rate was decreased from 29 breaths/min to 21 breaths/min
ECMO	Gupta *et al* [44]	Retrospective cohort	192 patients	47% had a decrease in DP, whereas 32 46% had an increase in DP, and 7% had no change in DP after ECMO initiation. Those with an increase in DP had a significantly longer stay on ECMO than those without; Higher DP 24 h after ECMO initiation was associated with an increase in 30-d mortality
ARDS	Del Sorbo *et al* [47]	Randomized crossover physiologic study	10 patients	A linear relationship was seen between the change in driving pressure and the concentration of IL-6
ECMO	Magunia *et al* [45]	Retrospective cohort	105 patients undergoing VV-ECMO	ΔP was greater than 15 mbar in non-survivors
ECMO and ARDS	Chiu *et al*[46]	Retrospective cohort	158 patients with severe ARDS on ECMO	After ECMO initiation, non-survivors had significantly higher dynamic DP until day 7 than survivors; Acute Physiology and Chronic Health Evaluation II score, ARDS duration before ECMO and mean driving pressure were independently associated with mortality
Surgical	Blank *et al*[49]	Retrospective cohort	1019 patients undergoing thoracic surgery with ventilation	DP was a risk factor for overall post-operative morbidity
Surgical	Neto *et al*[50]	Meta-analysis	17 randomized controlled trials, including 2250 post-operative patients	DP was associated with the development of postoperative pulmonary complications; An increase in the level of PEEP that resulted in an increase in DP was associated with more postoperative pulmonary complications
Surgical	Mathis *et al* [51]	Observational Cohort	4694 patients	10.9% experienced pulmonary complications
Surgical	Park *et al*[52]	Double-blind, randomized, controlled trial	292 patients	Melbourne Group Scale of at least 4 occurred in 8 of 145 patients in the DP group
	Li *et al*[71]	Systematic review	640 patients	The incidence of PPCS was lower and the compliance of the

		and meta-analysis		respiratory system was higher in the DP-oriented group during OLV
Obesity	De Jong *et al* [55]	Retrospective cohort	72% non-obese and 28% obese patients	The mortality rate at day 90 was 47% in the non-obese and 46% in the obese patients; In obese patients, driving pressure at day 1 was not significantly different
Pregnant	Lapinsky *et al* [60]	Prospective cohort	In 21 ICUs 69 patients requiring invasive mechanical ventilation, and 47 patients delivered while on the ventilator	Survivors had an average DP of < 14 cm H_2O; Maternal mortality rate of 17.5 %, and perinatal mortality rate of 15.4%; The mortality rate was lower than in the general COVID-19 population
Pediatric	Rauf *et al*[9]	Retrospective cohort study	380 children in the ICU	Children in the group with low ΔP (< 15 cm H_2O) had significantly lower median duration of ventilation, length of stay and ventilator-free days
ARDS	Yehya *et al* [61]	Prospective cohort study	544 children	DP was not an independent predictor of mortality
Pediatric	Schelven *et al* [13]	Prospective cohort study (secondary analysis)	222 children	Higher disease severity, MV indication, and increase in extubation time in patients with higher DPs
Heart Failure	Yang *et al*[67]	Retrospective cohort	632 patients	DP was independently associated with in-hospital mortality
No ARDS	Schmidt *et al* [10]	Retrospective cohort	622 patients	ΔP was not independently associated with hospital mortality

ARDS: Acute respiratory distress syndrome; PEEP: Positive end expiratory pressure; ICU: Intensive care unit; ΔP: Change in pressure; MV: Mechanical ventilation; DP: Driving pressure; OLV: One-lung ventilation; PPCS: Postoperative pulmonary complications; ECMO: Extracorporeal membrane oxygenation; PBW: Predicted body weight; COVID-19: Coronavirus disease 2019; RCT: Randomised controlled trials.

at play so that they can determine attributable risk. Further research on ARDS can benefit from using measurements such as esophageal manometry, as transpulmonary ΔP is a more accurate representation of the force being applied to the lung. An effort should be made to conduct more studies that include different pathologic states that lead to ARDS and clarify any variations in ΔP and ventilatory parameters.

In addition, more randomized controlled trials are needed to better understand the usefulness of ΔP in practice, establish causality, and determine its impact on long- and short-term outcomes. Further exploration of the impact of ΔP in various subsets of populations with varying etiologies is also needed. Basic science and physiological studies assessing the variability of pressures, lung volumes, oxygenation, and deformation of respiratory cells are needed to gain a more causal, sophisticated glance into cellular stress and strain[5].

Some up-and-coming trials that may provide further insight into the prospects and usefulness of ΔP were researched. Upon searching the term 'ΔP' in clinicaltrials.gov, many promising studies emerged that aim to elaborate on the role of ΔP in various situations. A few of them are described as follows.

ΔP limited ventilation for Patients With ARDS [ART-2-Trial ID: NCT02365038]; a multicenter pilot randomized control trial that is assessing the feasibility of limiting ΔP during ventilation of ARDS patients in one arm and employing the standard ventilatory guidance by ARDS Network strategy in the control arm. The tidal volume will be adjusted 3-8 mL/kg PBW to get target values of 13 cm H_2O in ΔPs calculated day 1 and day 3 of randomization.

Mechanical ventilation based on ΔP in lateral position (Trial ID: NCT04455789) A randomized, controlled, double-blind study of 60 patients undergoing total hip replacement surgery. The aim is to investigate the effects of different positions on ventilation utilizing traditional lung protective parameters in the control arm and a low ΔP arm. They aim to assess hemodynamic and respiratory values and overall postoperative outcomes.

ΔP during general anesthesia for open abdominal surgery (Trial ID: NCT03884543). A randomized multicenter double-blinded control trial to assess whether the application of high peep during mechanical ventilation to maintain low levels of ΔP helps prevent complications compared to standard low peep strategies. The study targets patients undergoing abdominal surgery who are at intermediate to high risk of pulmonary complications based on the ARISCAT score. These studies and many others hold strong promise in showing an appropriate application of ΔP and its impact in various settings.

CONCLUSION

ΔP has proven to be a highly significant metric when ventilating patients, particularly in ARDS. Adjusting for ΔP has shown improved clinical outcomes and fewer incidences of VILI. Considerations should be made to improve the accuracy of measurements and monitoring. Ongoing research should enhance our understanding of ΔP and how to best harness its potential in providing tailored, safe, and effective ventilation[3,4].

FOOTNOTES

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