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Transpulmonary Pressure–guided Ventilation to Attenuate Atelectrauma and Hyperinflation in Acute Lung Injury

The inherent appeal of using esophageal manometry to guide positive end-expiratory pressure (PEEP) titration lies in its ability to distinguish lung from chest wall mechanics. Transpulmonary pressure (P_L) is calculated as the pressure measured at the airway opening minus the pleural pressure, which is typically estimated via esophageal manometry. Lung injury termed "atelectrauma" may occur from high regional forces generated repeatedly during cyclic closure and reopening of small airways during tidal ventilation (1, 2). Negative P_L values (in which pleural pressure exceeds airway pressure) predispose to small airways closure and cause lung injury that in preclinical models, is attenuated with higher PEEP (3, 4).

In this issue of the *Journal*, Bastia and colleagues (pp. 969–976) highlight the potential for esophageal manometry to estimate P_L even in asymmetric lung injury (5). In their study, invasively ventilated pigs were subjected to unilateral lung injury via surfactant lavage and high tidal stretch instituted with temporary endobronchial blockade, occluding the contralateral lung. After injury was established, the bronchial blocker was removed, and respiratory mechanics were assessed in both hemithoraces at different amounts of PEEP. Pleural pressure was measured directly using air-filled balloon catheters inserted into the ventral and dorsal pleural spaces of the left and right hemithoraces, and it was

Supported in part by a grant from the NIH (R21-HL145506, to J.R.B.).

Originally Published in Press as DOI: 10.1164/rccm.202011-4116ED on November 23, 2020

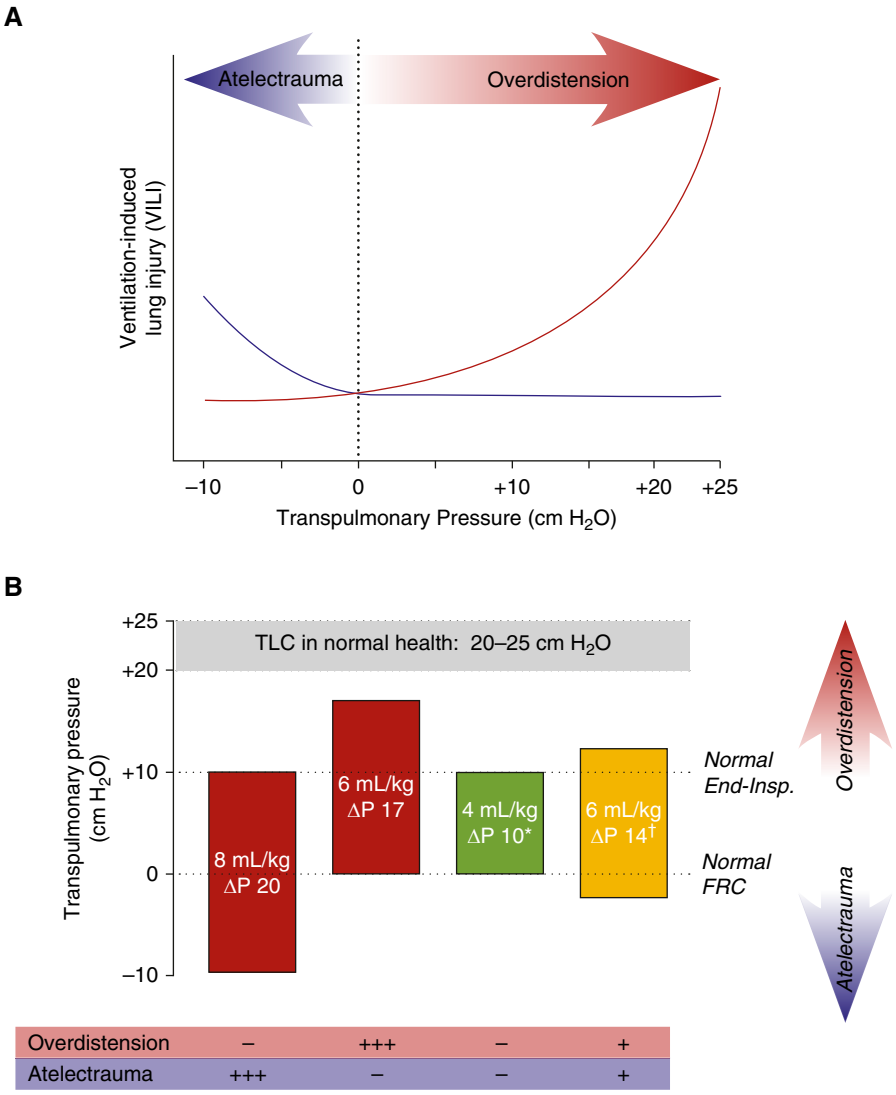

Figure 1. Transpulmonary pressure (P_L) to guide lung-protective ventilation. (*A*) Theoretical relationship of P_L with the competing risks of ventilation-induced lung injury (VILI) from overdistension and atelectrauma. The risk of clinically meaningful injury from overdistension exceeds that of atelectrauma. (*B*) Ventilator titration ideally would seek to attenuate both overdistension and atelectrauma in at-risk patients. Maximal lung protection may occur when positive end-expiratory pressure is set to achieve an end-expiratory P_L near 0 cm H_2O and V_T is targeted to a driving P_L of ⩽10–12 cm H_2O. Boxes reflect the range of P_L during tidal ventilation in a theoretical patient with severe acute respiratory distress syndrome. Red, yellow, and green colored boxes denote high, moderate, and low risk of VILI, respectively. In practice, patient susceptibility to biophysical injury may be a key determinant of the numerical threshold at which the risk of lung injury from overdistension exceeds that of atelectrauma. For reference, in the lean, healthy, spontaneously breathing adult, P_L is ~0 cm H_2O at FRC, 10 cm H_2O at end-inspiration during normal tidal breathing, and 20–25 cm H_2O at TLC. Reported V_T is in ml/kg predicted body weight, and ΔP is in cm H_2O. *If gas exchange permits; †if V_T cannot be lowered. ΔP = driving pressure; End-Insp. = end-inspiration.

also estimated with esophageal manometry. Electrical impedance tomography was used to evaluate heterogeneous insufflation.

Vertical pleural pressure gradients were observed as previously described (6, 7), but no significant difference in pleural pressure of the left versus the right hemithorax was found, regardless of which lung was injured. These findings are expected given that lung injury induced via the airway should not alter chest wall mechanical properties. Normally, mechanical coupling of the left and right hemithoracic pleural spaces occurs via *1*) mechanical coupling of the left and right rib cages with symmetrical movement during respirations and *2*) compliance of mediastinal structures separating the hemithoraces. In contrast to unilateral lung injury, decreased mediastinal compliance can create asymmetric hemithoracic chest wall mechanics, as may occur with mediastinal fibrosis resulting from thoracic surgery or chest radiation therapy, for example (8).

In their swine model, esophageal pressure corresponded closely with posterior pleural pressure. However, in humans, esophageal pressure approximates the midthoracic pleural pressure, a contrast explained by differences in swine versus human chest wall shape and anatomic position of the esophagus in the thorax (9).

Bastia and colleagues also demonstrated asymmetric insufflation of injured versus noninjured lungs, a direct result of differences in lung compliance created by unilateral injury. Importantly, heterogeneous insufflation was attenuated with higher PEEP *at the expense of increasing hyperinflation*, which was most pronounced in the noninjured lung. Intriguingly, PEEP titrated to achieve P_L near 0 cm H_2O appeared to minimize the competing effects of end-expiratory lung collapse and hyperinflation. Pronounced collapse occurred particularly in the injured lung when end-expiratory P_L was negative (<0 cm H_2O), presumably because of gravitational effects on increased lung mass from cell-rich edema infiltration, as well as effects of surfactant depletion. The noninjured lung, being more compliant, was more susceptible to hyperinflation particularly when end-expiratory P_L was positive (>0 cm H_2O).

The surfactant depletion model employed in this study might amplify the degree of collapse observed with negative P_L, and no measures of lung injury were reported. Also, reports of regional P_L should be viewed skeptically because of small airway closure and flooded alveoli, as discussed previously in this journal (10). Nevertheless, these findings highlight the potential folly of aggressive PEEP titration without regard for lung stress or strain, particularly in heterogeneous lung injury. The preponderance of existing human and preclinical data indicates that lung injury from overdistension is far more detrimental than that from atelectrauma. Thus, any potential lung-protective benefit from higher PEEP might only be evident when the risk of end-tidal overdistension is minimized simultaneously.

One could envision that an ideal PEEP titration strategy in acute lung injury might begin by targeting P_L near 0 cm H_2O at end-expiration to attenuate atelectrauma (Figure 1). Some measure of inspiratory stress or strain (e.g., airway or transpulmonary driving pressure, end-inspiratory P_L, or electrical impedance tomography–derived strain) (11) might then be used to determine whether protective ventilation can be attained at a V_T of 6 ml/kg predicted body weight without significant hyperinflation. If hyperinflation persists, V_T would be lowered until hyperinflation abates. If gas exchange impairment precludes further reduction in V_T despite increasing respiratory rate, then either *1*) PEEP would be lowered, and negative end-expiratory P_L would tolerated in recognition of the greater contribution of hyperinflation to clinically significant lung injury or *2*) if deemed appropriate, extracorporeal gas exchange could be considered to enable further reduction in V_T when appropriate.

Such a PEEP strategy has not been tested in a clinical trial. In the EPVent-2 trial of moderate to severe acute respiratory distress syndrome (12), esophageal pressure–guided PEEP was targeted to an end-expiratory P_L between 0 cm H_2O and $+6$ cm H_2O depending on the F_{IO_2} requirement. Although speculative, it is conceivable that some patients in this protocol experienced overdistension that countered the protective effects against atelectrauma. The EPVent-2 protocol did prescribe limits to "peak stress," prohibiting end-inspiratory P_L from exceeding 20 cm H_2O, but increasing evidence suggests that a lower end-inspiratory P_L might attenuate overdistension further (11, 13).

Although translation to demonstrable clinical benefit has proven elusive, preclinical studies continue to suggest a protective role for precise PEEP titration in severe acute lung injury. Competing effects of overdistension and atelectrauma with higher and lower PEEP, respectively, almost certainly have contributed to past unsuccessful trials. So too has phenotypic heterogeneity, including but not limited to differences in mechanical and biological susceptibility to ventilation-induced lung injury (14, 15). Future trials should explicitly confront the competing effects of PEEP and the inherent phenotypic heterogeneity of acute respiratory distress syndrome to provide the best chance for identifying the optimal PEEP titration strategy to maximize clinical benefit. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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Defining the Clinical Utility of the Lung Clearance Index
Are We There Yet?

The last decade has witnessed dramatic improvements in cystic fibrosis (CF) therapeutics with the introduction of a novel class of drugs known collectively as "CFTR modulators" (1). Most recently, a combination of modulators has made it possible to eventually offer "highly effective modulator therapy" (HEMT) to an estimated 90% of the U.S. population with CF (2, 3). Also, the data accumulated from multiple clinical trials has provided clear evidence for what constitutes as a disease-modifying effect in the natural history of CF. It is clearly recognized that in order for patients with CF, in particular young children, to continue to benefit from innovative therapies such as HEMT, there is a need to target therapies before irreversible lung damage has occurred. However, the ability to avert lung disease progression in CF is contingent on early detection and timely intervention. This will require the availability of tools that are both sensitive and feasible in the routine clinical setting. It is now well established that lung disease begins very early in life in children with CF (4, 5), with impaired mucociliary clearance being a hallmark and at the root of all the respiratory complications that patients experience (6, 7). Therefore, great attention has historically been paid to the accurate detection and monitoring of airway obstruction as a reflection of CF airway disease at all stages of disease progression. CF clinicians are highly familiarized with the use of spirometry, and in particular the FEV_1, as a useful tool for the detection of airway obstruction and to support clinical decision-making. However, an already large body of evidence has demonstrated that significant lung disease can be present in the face of a normal FEV_1 (8, 9). This fact, in addition to the robust and persistent changes seen in FEV_1 in response to HEMT, have identified a need to bring to the clinic assessment tools that will be more sensitive to the presence of airway disease. Perhaps of greatest importance is also the ability of such a tool to detect detrimental changes as well as support therapeutic intervention and assist in monitoring the response to such an intervention to evaluate its effects.

As a result, an array of functional and image-testing modalities have been and continue to be actively investigated on CF for their ability to provide an accurate assessment of airway disease (10–14). Thanks to technological advances, parameters obtained from the multiple-breath washout technique have emerged as providing an alternative, sensitive assessment of airway function. Among the parameters that can be estimated from the multiple-breath washout the number of FRC volume turnovers required to clear a tracer from the lungs or Lung Clearance Index (LCI) has demonstrated great sensitivity to early airway disease (15). The LCI provides a metric for the degree of heterogeneity in gas distribution present throughout the tracheobronchial tree, a key aspect of CF pathophysiology. Intensive clinical research conducted over the past few years has already demonstrated the value of the LCI in the research setting, helping to establish it as an important endpoint for clinical trials (16–18). However, there are still important gaps in the information required to understand its potential role in the clinical setting. In this issue of the *Journal*, Perrem and colleagues (pp. 977–986) provide evidence from a two-center prospective study on the value of the LCI as an outcome measure when applied to the routine clinical setting in the care of children with CF (19). The focus of the study was on respiratory events experienced over a 2-year period, and although clinical decisions were not formalized by the study protocol or guided by the measurements performed in the children that participated in the study, there are several valuable insights gained from the study results. Some important considerations need to be taken into account to interpret their results in their full context. First, as it has progressively become an expectation for children with CF, this cohort had, for the most part, fairly normal pulmonary function by spirometry and morbidity features typically associated with CF such as weight loss, *Pseudomonas* infection, hemoptysis, and radiographic changes that were of rare occurrence. Second, the investigators had to develop a categorization scheme to qualify the respiratory events experienced by these children, as many would not have fulfilled the classic definitions of CF pulmonary exacerbation but still had changes in their treatment regimens, primarily through courses of antibiotics.

Originally Published in Press as DOI: 10.1164/rccm.202010-3899ED on November 12, 2020