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Should mechanical ventilation be guided by esophageal pressure measurements?

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Abstract

Purpose of review—Despite the well recognized role of mechanical ventilation in lung injury, appropriate surrogate markers to guide titration of ventilator settings remain elusive. One would like to strike a balance between protecting aerated units from overdistension while recruiting unstable units, thereby reducing tissue damage associated with their cyclic recruitment and derecruitment. To do so requires some estimate of the topographical distribution of parenchymal stress and strain.

Recent findings—Recent studies have highlighted the importance of chest wall recoil and its effect on pleural pressure (P_{pl}) in determining lung stress. Although esophageal pressure (P_{es}) has traditionally been used to measure the average P_{pl} in normal upright patients, in recumbent acute lung injury/acute respiratory distress syndrome patients P_{es} -based estimates of P_{pl} are subject to untestable assumptions. Nevertheless, P_{es} measurements in recumbent patients with injured lungs strongly suggest that P_{pl} over dependent parts of the lung can exceed airway pressure by substantial amounts. Moreover, results of a pilot study in which P_{es} was used to titrate positive end-expiratory pressure (PEEP) suggest clinical benefit.

Summary—Notwithstanding its theoretical limitations, esophageal manometry has shown promise in PEEP titration and deserves further evaluation in a larger trial on patients with injured lungs.

Keywords

acute lung injury/acute respiratory distress syndrome; esophageal pressure; lung stress; positive end-expiratory pressure; ventilator-induced lung injury

Introduction

Despite advances in the understanding and treatment of acute lung injury (ALI) and its more severe form, the acute respiratory distress syndrome (ARDS), incidence and mortality remain high [1,2]. Evidence has been accumulating for the past 50 years that mechanical ventilation, which is often an important part of therapy in these patients, can cause or amplify damage in the injured lung [3]. Two of the attributes of the ALI/ARDS lung that increase its susceptibility to ventilator-induced lung injury (VILI) include: the number of alveoli that can expand during inspiration is decreased ('baby lung' [4]) placing them at increased risk for overdistension; and repeated opening and collapse of small airways and

alveolar ducts blocked by air–liquid interfaces and foam can cause deformation and wounding of lining cells [5–8].

Proposed lung protective mechanical ventilation strategies include limiting tidal volume to prevent overdistension and applying positive end-expiratory pressure (PEEP) to avoid cyclic derecruitment and achieve more uniform lung expansion. Indeed the ARDSnet trial showed that patients ventilated with a tidal volume of 6 ml/kg of ideal body weight had a 22% relative reduction in mortality compared to patients receiving 12 ml/kg [9]. On the other hand, although numerous animal studies have shown beneficial effects from PEEP application [10–14], randomized clinical trials in adults with ARDS failed to show improvement in relevant outcomes with higher PEEP levels [15–17]. A recent meta-analysis of 2299 patients with ALI/ARDS concluded that treatment with higher versus lower levels of PEEP was not associated with improved hospital survival [18**]. Higher PEEP levels were, however, associated with improved survival among the subgroup of patients with ARDS. Given the high pretest probability that PEEP affords lung protection from injurious stress associated with the cyclic ‘opening and collapse’ of unstable lung units, the three large clinical trials have not silenced the ‘best PEEP’ debate [15–17]. A common criticism leveled at all three is doubt about the validity of the surrogate endpoints used to titrate PEEP, namely oxygenation within an airway occlusion pressure (plateau pressure, P_{plat}) limit of 30 cmH₂O or less [15,16]. This criticism has gained credibility in light of recent esophageal manometry derived evidence, which strongly suggests that in recumbent patients with injured lungs airway pressure (P_{aw}) is an inadequate and often biased measure of lung stress [19].

Motivated by this controversy we will review the determinants of the topographical distributions of pleural pressure (P_{pl}) and lung stress, as reflected in transpulmonary pressure (P_{tp}), in health and disease; articulate how the therapeutic objectives of lung protective mechanical ventilation intersect with the distributions of lung stress; present the assumptions and experimental evidence that esophageal pressure (P_{es}) approximates P_{pl} and together with P_{aw} informs about average lung stress; and review the clinical evidence pertaining to P_{es} -guided ventilator management of patients with ALI and ARDS.

Ventilator management objectives and their dependence on the topographical distribution of parenchymal stress and strain

Engineering terms have been used to describe the mechanical properties of tissue and quantify its deformation. ‘Stress’ is defined as the counterforce per unit of cross-sectional area of a structure that balances and reacts to an external load [20]. The associated deformation of the structure relative to its resting state is called ‘strain’ [20]. Specifically in the lung, stress is expressed by P_{tp} which equals the difference between alveolar pressure (P_{alv}) and P_{pl} . Although ideally for strain computation the reference state is the unstressed state, the lung is always prestressed, that is P_{tp} is not zero.

The topographical distribution of P_{pl} of the normal lung is not uniform due to shape-matching constraints between two gravitationally deformed elastic solids: the lung and chest wall [21*,22]. If one wanted to restore lung shape out of the chest at the same volume, one would have to apply a topographically nonuniform surface pressure, similar to P_{pl} distribution *in situ*. The weight of the heart and the effect of the abdomen on the diaphragm and rib cage also affect volume distribution along with small-scale heterogeneity that still has not been explained by any gravitational mechanism [21*,23].

The weight of the healthy lung only has minor influence, but in the case of the ‘heavy’ injured lung P_{pl} gradient would be expected to increase. Near resting volume the normal

lung is fluid like and regional variability in P_{pl} changes is relatively small, thus allowing P_{es} to reflect an effective average P_{pl} . At high volumes the lung becomes stiff and even small deviations from the shape that would have been observed out of the thoracic cavity produce large local stress gradients. In the injured lung of ARDS patients alveolar flooding, occlusion of small airways by liquid plugs, small-scale variability in surface tension, and varying degrees of gas absorption atelectasis make stress distribution even more heterogeneous [6]. Variations in shape or volume change the projected area over which distending forces of tissue attachments are distributed, thus changing local stress. Due to interdependence tissue attachments between neighboring units with different pressure carry a shear stress that is substantially greater than average P_{tp} [24].

Patients suffering from ALI/ARDS usually have multiple reasons for altered chest wall mechanics, determined by the complex interaction of passive mechanical properties of the rib cage, the diaphragm, and the abdomen, the most obvious being gravitational and shape changes due to recumbence [25,26]. Moreover, abdominal diseases such as bowel distension, hemoperitoneum and ascites are common in patients with ARDS [25,26] and up to 58% of critically ill patients admitted to medical and surgical ICUs were found to have intraabdominal hypertension [27–29]. Obesity, another common problem among ICU patients, has also been linked with increased P_{pl} affecting lung volume [26,30,31**]. Resuscitation with large fluid volumes and the resulting tissue edema, a frequent occurrence in ARDS patients, was associated with increased P_{es} , and lung volume restriction in pigs [32].

Due to the heterogeneous distribution of P_{pl} and hence lung stress and strain, injury mechanisms differ between different regions of the same lung. Since ARDS lungs contain normally aerated, poorly aerated and non-aerated lung units, the therapeutic objective of mechanical ventilation is to strike a balance between protecting aerated units from overdistension while preventing derecruitment of unstable units, and thereby reducing tissue damage associated with cyclic opening and collapse. In subsequent sections of this review, we will discuss how esophageal manometry can be helpful in achieving these objectives. Nevertheless, it must be acknowledged that the relative importance of overdistension as opposed to cyclic opening and collapse on lung repair and patient relevant outcomes remain highly controversial.

Airway pressure as a surrogate of lung stress

In everyday clinical practice, P_{aw} is used to monitor respiratory mechanics. The pressure applied by the ventilator is either stored as elastic pressure or dissipated as resistive pressure used to overcome ventilator and tracheal tubing and airway resistance [5,33]. During static conditions in the absence of airflow, P_{aw} represents the pressure necessary to overcome the elastic recoil of the respiratory system and equals P_{alv} . P_{aw} during an end-inspiratory occlusion (P_{plat}) is used as a surrogate marker of maximum lung distension and P_{aw} during an end-expiratory occlusion (PEEP) as an indicator of end-expiratory elastic pressure. The elastance of the respiratory system (E_{rs}), however, equals the sum of the elastance of the lung (E_L) and the chest wall (E_{CW}) ($E_{rs} = E_L + E_{CW}$) and P_{aw} equals the sum of P_{tp} and P_{pl} ($P_{aw} = P_{tp} + P_{pl}$), which distend the lung and chest wall respectively [25,33]. From the above equations, $P_{tp} = P_{aw} \times E_L/E_{rs}$ and $P_{pl} = P_{aw} \times E_{CW}/E_{rs}$, that is the amount of P_{aw} that is spent to inflate the lung depends on the characteristics of the chest wall [25,26]. P_{tp} is the true indicator of end-inspiratory lung stress and P_{tp} equals the difference between P_{alv} and P_{pl} ($P_{tp} = P_{plat} - P_{pl}$). Using P_{plat} as a surrogate marker of lung stress, therefore, ignores the contribution of the chest wall [25,33]. Sequential increments in intraabdominal pressure by CO₂ insufflation in pigs, for example, caused an increase in P_{lat} , which was not accompanied by an increase in P_{tp} due to the concomitant increase in P_{es} [34*].

The importance of P_{tp} versus P_{aw} in inducing lung injury was demonstrated in an experimental study in which lowering end-expiratory P_{tp} at fixed P_{aw} -PEEP by chest wall constriction (and P_{pl} increase) in a rat model of saline lavage plus VILI reduced end-expiratory lung volume, and exacerbated VILI [35*,36]. On the contrary, in an older study in rabbits, chest wall restriction with a plaster cast led to volume limitation and prevented microvascular alterations at the same peak P_{aw} [37]. Although these results at first appear conflicting, in reality they underscore the importance of measuring individual patient respiratory mechanics since similar airway pressures can be protective or harmful depending on the resulting P_{tp} , which is in turn dictated by P_{pl} .

Esophageal pressure derived estimates of lung and chest wall mechanics

A variety of methods have been used in animals for directly measuring P_{pl} , the force per unit area of pleural surface, but none is universally accepted. Introduction of a measuring device that produces a local deformation of the visceral pleura, any air entering the pleural space or removal of intercostal muscle to puncture the parietal pleura may all drastically alter local P_{pl} [38]. As it is not feasible to directly measure P_{pl} in humans most data have been obtained from esophageal manometry with a balloon-tipped catheter [23,39]. There is general agreement that P_{es} may be used to estimate P_{pl} change during breathing in healthy upright patients [39]. For P_{es} to accurately reflect P_{pl} , the pressure measured in the esophageal balloon has to accurately represent the pressure in the esophagus; the transmural pressure of the esophagus should be zero; the esophagus should not be compressed by the heart or other mediastinal structures; and the pressure in the mediastinum surrounding the esophagus should be equal to P_{pl} [40,41]. P_{es} can exhibit variations unrelated to P_{pl} depending on the volume of air inside the balloon [39], on the position of the balloon in the esophagus [42], or on postural artifacts [43]. With too little air the positive pressure in the esophagus will empty the balloon and the measured pressure will underestimate P_{es} . Too much air will distend the esophagus or stress the balloon and the measured pressure will overestimate P_{es} [44**]. Pressure within the esophagus varies considerably partly due to gradients in P_{pl} and local differences in P_{es} unrelated to P_{pl} [39,44**]. The position of the balloon is considered optimal when the change in P_{aw} equals the change in P_{es} as a patient makes expiratory or inspiratory efforts against an occluded airway [45]. This criterion is generally met in the lower third of the esophagus, approximately 10 cm above the gastroesophageal junction, in upright patients, but the optimal positioning of the balloon in supine patients has been questioned [46]. In a study of anesthetized spontaneously breathing patients the optimal location was variable and unpredictable [46]. Moreover, P_{es} has repeatedly been found to increase upon recumbence [43,47,48]. Washko *et al.* [43] studied the magnitude and variability of postural effects in 10 healthy patients. Approximately 58% of the reduction in P_{tp} upon recumbence was due to the decrease in lung volume and the remaining (2.9 cmH₂O) was attributed to mediastinal weight. The authors concluded that subtracting a 3 cmH₂O correction from P_{es} would account for mediastinal artifact. The 95% confidence interval for this correction, however, was -1 to 7 cmH₂O and standard deviation was 2.1 cmH₂O, indicating great variability in this artifact even within normal patients.

Although the potential role of the rate and amplitude of stress change is still unclear, lung stress at end-inspiration is usually perceived as the P_{tp} responsible for injury. End-inspiratory P_{pl} is needed to calculate the corresponding P_{tp} . Reduced chest wall compliance (C_{CW}) is considered by many synonymous to increased P_{pl} , but the two need not coexist. C_{CW} refers to the change in elastic recoil pressure of the chest and may well be normal despite elevated values of elastic recoil (P_{pl}). Restrictive respiratory changes caused by obesity are a characteristic example of reductions in lung volume attributed to elevated P_{pl} and yet several studies have reported normal C_{CW} in obese patients [31**,49,50]. Recently, Behazin *et al.* [31**] measured resting values of P_{es} in anesthetized, paralyzed obese patients

for the first time. P_{es} was high, often substantially above atmospheric pressure. Although obese patients were characterized by lower respiratory system and lung compliance, C_{CW} was usually normal. Normal C_{CW} is consistent with ‘mass loading’ rather than ‘stiffening’ of the chest by elastic loading, that is the chest wall pressure–volume curve exhibits a rightward shift (higher pressures at any lung volume) without being stiffer (without a decrease in slope) [51]. This underlines the importance of estimating P_{pl} when evaluating lung stress and not simply changes in P_{pl} , which may be within normal limits, although the latter would eliminate some of the inherent biases of P_{es} measurements as discussed later.

Several studies have attempted to calculate lung stress using esophageal manometry in ALI/ARDS patients. In an observational study of ALI/ARDS patients, P_{es} averaged 17.5 ± 5.7 cmH₂O at end-expiration and 21.2 ± 7.7 cmH₂O at end-inflation and was not significantly correlated with E_{CW} [19]. Estimated P_{tp} was 1.5 ± 6.3 cmH₂O at end-expiration and 18.4 ± 10.2 cmH₂O during end-inspiratory occlusion. Only 24% of the variance in P_{tp} was explained by P_{aw} and 52% was due to variation in P_{es} . Estimated end-expiratory P_{tp} was negative in a large number of patients even at high PEEP, which was interpreted as evidence that many patients have cyclic collapse of lung units when ventilated with standard settings. Taking into account that the forces responsible for lung parenchymal folding are presumably derived from surface tension and the resistance of alveolar walls to folding is small, transmural alveolar pressure of aerated lung units that communicate freely with central airways is expected to be positive at all lung volumes [21*]. The authors reasoned that a negative P_{tp} does not imply a negative elastic recoil pressure of the lung. It may be attributed to airway closure that prevents P_{alv} from equilibrating with P_{aw} causing underestimation of P_{alv} by P_{aw} . Alternatively, P_{tp} is biased by units that are closed and extrinsically compressed by pleural fluid or the weight of abdominal contents. Moreover, P_{pl} is probably lower and P_{tp} higher in the nondependent lung.

Chiumello *et al.* [52] calculated lung stress as the difference in P_{tp} between functional residual capacity (FRC) and end-inspiration and found that a given applied P_{aw} produced largely variable stress due to the variability of the E_L -to- E_{Ts} ratio. This approach has the advantage that assuming the artifact is constant at the two lung volumes, the artifacts could arithmetically cancel out in the calculation of dP_{tp} [53]. However, only if prestress is low, can the amplitude of stress change be informative of end-inspiratory stress. Loring *et al.* [54**] confirmed the findings of negative P_{tp} despite high levels of PEEP in ALI/ARDS patients and found close correlations between end-expiratory P_{es} , P_{ga} and P_{blad} . P_{es} averaged 18.6 ± 4.7 cmH₂O during end-expiratory occlusion and 22.3 ± 5.0 cmH₂O during end-inspiratory occlusion and was not correlated with E_{CW} . According to the authors the association of high P_{es} with commensurately high P_{ga} and P_{blad} , which are not subject to the effects of mediastinal weight and inhomogeneous lung mechanics, indicates that high P_{es} values reflect real elevations in intrathoracic pressures. P_{tp} at end-inspiration and end-expiration was largely influenced by P_{es} . Lung parenchymal stress at end inflation was most importantly determined by the pres-tress before inflation and was much less than stress inferred from P_{plat} and E_L and E_{CW} . In their study, lung stress calculated by the Chiumello equation was completely different from end-inspiratory stress calculated as P_{tp} at end-inspiration. Identical changes in stress may result in completely different end-inspiratory parenchymal stress after a tidal inflation from a low or high initial stress [54**].

Given the above uncertainties in P_{es} estimates of P_{pl} , most of which are practically untestable, several questions arise. What is the required accuracy of the technique for clinical decision making? Some argue P_{es} values in ALI/ARDS patients are much greater than the small artifact minimizing its influence on the calculated value. Is the knowledge of an average P_{pl} enough to guide mechanical ventilation? P_{alv} is also needed to calculate P_{tp} . Using P_{aw} as an estimate of P_{alv} during static conditions assumes open airways and freely

communicating alveoli, which is highly unlikely in injured lungs. Moreover, as already discussed, stress related injury mechanisms differ in different parts of the lung. Ideally one would like to have an elastography map in order to limit stress in overdistended areas and increase it in the collapsed parts. Is a strategy which embraces the open lung concept at the risk of overinflation superior to the one that seeks to minimize P_{plat} while accepting less than full alveolar recruitment? The chance that pressure anywhere along the lumen of the esophagus, especially in dependent areas surrounded by pleural effusion, informs about average lung stress is slim. Even if P_{es} accurately reflects P_{pl} at midlung height, titrating PEEP to the lowest value of P_{es} in dependent areas might maintain inflation of the lungs at end-expiration, but will inevitably lead to over-distension of nondependent parts at end-inspiration.

Esophageal pressure guided mechanical ventilation in acute lung injury/ acute respiratory distress syndrome

The idea of customizing lung protective mechanical ventilation according to P_{tp} is very appealing [41]. For all the reasons detailed above, however, even if P_{es} accurately reflects P_{pl} at midlung height, P_{pl} in regions above and below would be lower and higher respectively and titration of mechanical ventilation according to P_{es} would lead to overinflation of nondependent and under recruitment of dependent regions. The only relevant clinical trial to date compared titrating PEEP to maintain positive P_{tp} at end-expiration to the standardized PEEP/ FiO_2 tables of the ARDS Network trial [55]. As expected this strategy led to higher PEEP and better oxygenation in the intervention group. The improvement in gas exchange was paralleled by improvement in lung mechanics and a strong trend toward favorable clinical outcomes, such as shorter durations of mechanical ventilation and lower 28-day and 6-month mortality. P_{plat} was elevated in the intervention group, in some cases more than 30 cmH₂O, but end-inspiratory P_{tp} was not significantly different between the groups.

Conclusion

ARDS-injured lungs are characterized by large local stress gradients that render them particularly susceptible to VILI. Knowledge of intrathoracic pressure improves a provider's ability to manage the risk of overinflation relative to that of underrecruitment. While the unknown bias of esophageal manometry derived P_{pl} and hence stress estimates of aerated lung units remain of concern, based on the strength of the rationale and the results of initial clinical studies, the technique clearly deserves formal evaluation in an appropriately powered randomized controlled clinical trial.

Acknowledgments

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 314).

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Key points

- Airway pressure is a poor surrogate of lung stress (airway minus pleural pressure) because it ignores the effect of chest recoil.
- Pleural surface pressure distribution is not uniform, especially in ALI/ARDS patients.
- One would ideally like to know the topographical distribution of transpulmonary pressure in order to titrate mechanical ventilation, because injury mechanisms differ at different parts of the lung.
- To date, only an estimate of an average pleural pressure can be inferred from pressure measurements in the esophagus or alternatively in bladder or the stomach and is subject to many untestable assumptions and artifacts.
- Favorable results of a single center study using esophageal pressure measurements to adjust positive end-expiratory pressure in order to maintain positive transpulmonary pressure warrant further trials.