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## The Promises and Problems of Transpulmonary Pressure Measurements in ARDS

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### Abstract

**Purpose of Review**—The optimal strategy for assessing and preventing ventilator induced lung injury in the acute respiratory distress syndrome (ARDS) is controversial. Recent investigative efforts have focused on personalizing ventilator settings to individual respiratory mechanics. This review examines the strengths and weaknesses of using transpulmonary pressure measurements to guide ventilator management in ARDS.

**Recent findings**—Recent clinical studies suggest that adjusting ventilator settings based on transpulmonary pressure measurements is feasible, may improve oxygenation, and reduce ventilator induced lung injury

**Summary**—The measurement of transpulmonary pressure relies upon esophageal manometry, which requires the acceptance of several assumptions and potential errors. Notably, this includes the ability of localized esophageal pressures to represent global pleural pressure. Recent investigations demonstrated improved oxygenation in ARDS patients when PEEP was adjusted to target a specific end-inspiratory or end-expiratory transpulmonary pressures. However, there are different methods for estimating transpulmonary pressure and different goals for PEEP titration among recent studies. More research is needed to refine techniques for the estimation and utilization of transpulmonary pressure to guide ventilator settings in ARDS patients.

### Keywords

acute respiratory distress syndrome; transpulmonary pressure; positive end-expiratory pressure; esophageal pressure

### Introduction

Mechanical ventilation of patients with acute respiratory distress syndrome (ARDS) may contribute to morbidity and mortality by causing ventilator-induced lung injury (VILI). VILI may develop from excessive pressure and volume during inspiration causing injurious stretching (overdistention) in the lung parenchyma.(1, 2) Other mechanisms of VILI occur when there is too little airway pressure and volume during exhalation. This may cause cyclic

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alveolar recruitment and derecruitment with each tidal breath or excessive tension in alveolar septae at margins between aerated and non-aerated lung.(3, 4)

As mechanical ventilation is critical for survival for many ARDS patients, numerous efforts over the past 25 years have been directed towards minimizing VILI. Many lung protective strategies utilize the pressure at the airway opening ( $P_{ao}$ ) to monitor the potential for VILI. For example, the NIH ARDS Network lower tidal volume protocol utilizes inspiratory plateau pressure to guide adjustments to tidal volume.(5) As the limitations of airway pressure alone to assess VILI have become more evident, some have suggested that estimating transpulmonary pressure ( $P_{TP}$ ) would be a better approach to guide ventilator management. This review examines the considerations for and against the use of  $P_{TP}$  measurements in ARDS.

## Airway Pressure Can Be Misleading

The transmural pressure of the lung ( $P_{tm,L}$ ), which represents stress in the lung parenchyma, is alveolar pressure minus pleural pressure, ( $P_{tm,L} = P_{alv} - P_{pl}$ ). During most static conditions, the alveolar transmural and transpulmonary pressure ( $P_{TP} = P_{ao} - P_{pl}$ ) are the same, since alveolar and airway pressures should be in equilibrium in the absence of airflow. However, airway pressure alone can misrepresent the stress on lung parenchyma because several variables affect it independent of injurious mechanical forces in the lung. During mechanical ventilation, airway pressure distends the lung and the chest wall in series. Increases in chest wall elastance, as with chest wall edema, kyphoscoliosis, and intra-abdominal hypertension, are usually associated with increases in pleural pressure, as more force is necessary to distend the chest wall. Thus, depending on the pleural pressure, the same measured  $P_{ao}$  can be associated with considerably different  $P_{TP}$  and consequently have considerably different implications for injury to the lung. (FIGURE 1)

## $P_{TP}$ to Monitor Potential for VILI

The use of  $P_{TP}$  is a physiologically appealing approach to reduce VILI from high volumes and pressures during inspiration and low volumes and pressures during expiration. The injurious forces that cause alveolar overdistention are correlated directly with the peak inspiratory  $P_{TP}$ , and the trauma from recurrent alveolar collapse and re-opening is related to the minimum end-expiratory  $P_{TP}$ . Thus, knowledge of the  $P_{TP}$  at end-inspiration and end-expiration, rather than airway pressure alone, could allow mechanical ventilator settings to be customized for each patient to minimize both causes of VILI.

Many intensive care physicians have adopted a strategy for mechanical ventilation in ARDS that utilizes tidal volumes of approximately 6ml/kg of predicted body weight and plateau pressures less than 30 cm H<sub>2</sub>O.(5) However, these measures may be insufficient to minimize VILI from overdistention in some patients because  $P_{TP}$  and lung stress may exceed safe limits on these settings during inspiration.(6-8)

Moreover, there is still no consensus for how to select optimal PEEP levels. Although studies in animal models suggest that higher PEEP levels are beneficial (2, 3, 9), this was not been corroborated in three recent randomized clinical trials.(10-12) However, these three

trials applied uniform strategies for higher PEEP in all patients randomized to receive higher PEEP, rather than tailoring PEEP levels to their specific lung and chest wall mechanics. If  $P_{TP}$  was known, then tidal volumes and PEEP could be titrated to individuals' respiratory system mechanics to prevent alveolar overdistention or to promote lung recruitment and limit cyclic collapse. In this fashion, at the same measured  $P_{ao}$ , patients with high chest wall elastance, high pleural pressures and low  $P_{TP}$  could receive higher levels of PEEP; and patients with normal chest wall elastance, low pleural pressures and high  $P_{TP}$  could receive lower tidal volumes or PEEP.(13) Thus, the use of  $P_{TP}$  to guide ventilator management in ARDS is intellectually attractive. However, the limitations of utilizing  $P_{TP}$  for this purpose must be understood before conclusions regarding its clinical value can be determined.

## How to Measure Pleural Pressure

The major obstacle to measuring  $P_{TP}$  is finding a practical and accurate method for estimating pleural pressure. Theoretically, pleural pressure can be measured by inserting a pressure monitoring device directly into the pleural space.(14) However, this technique is invasive and fraught with potential complications. Moreover, a device introduced into the pleural space alters the pressure in that space. The most commonly used method for estimating pleural pressure is esophageal manometry. Esophageal pressures ( $P_{es}$ ) were frequently employed in studies of respiratory mechanics in the 1950-1960s.(14-17) An air-filled catheter with a long thin-walled balloon near its distal end is inserted through the nose and positioned into the lower third of the esophagus.  $P_{es}$  has been considered representative of average pleural pressure surrounding the lung in upright, healthy individuals.(15, 16, 18) There is skepticism, however, in extrapolating the validity of  $P_{es}$  as a surrogate for pleural pressure to mechanically ventilated supine patients with ARDS.(19, 20)

## Sources of error in measuring pleural pressure

There are several sources of error in the estimation of pleural pressure from esophageal manometry. The pressure measured in the esophageal balloon may be affected by elastic recoil of the balloon, elastic recoil of the esophagus, esophageal muscle tone, and pressure transmitted from surrounding structures. (FIGURE 2) Because of gravitational forces, there is a vertical gradient of pleural pressure in both the upright and supine positions. Esophageal pressure correlates best with pleural pressure in the middle of this gravitational plane in either position, but the relationship between the esophageal and pleural pressure is inconsistent between different subjects.(14) Early studies also demonstrated significant variability in the relationship between esophageal and pleural pressures when subjects changed from the upright to supine position, probably because of cephalad movement of the diaphragm and the weight of the mediastinal contents.(14, 15, 18)

Washko and colleagues assessed effects of body position change (erect to supine) in 10 healthy individuals and found that  $P_{es}$  consistently increased in the supine position.(21) They suggested that a constant correction factor of 3 cm H<sub>2</sub>O could be added to  $P_{TP}$ , calculated from  $P_{ao} - P_{es}$ , to account for the weight of the mediastinum and movement of the diaphragm in the supine position. However, there was substantial inter-individual variability of this correction factor (95% confidence interval -1 - +7 cm H<sub>2</sub>O), and it was obtained in normal individuals.(21) Variability may be considerably greater in patients with

consolidated lungs, pleural effusions, cardiomegaly, and abdominal distention, introducing even more error into the estimation of  $P_{TP}$  based on  $P_{es}$ .

Rather than using the direct measurement of  $P_{es}$  with an assumed correction factor, Gattinoni and colleagues proposed an elastance-derived calculation of pleural pressure. This allows the absolute value of esophageal pressure to be ignored, as the chest wall elastance is calculated from only the change in esophageal pressure from end-inspiration to end-

expiration ( $E_{cw} = \frac{P_{es,insp} - P_{es,exp}}{V_T}$ ). (22) Elastance of the respiratory system ( $E_{rs}$ ) is calculated from the change in plateau pressure minus PEEP divided by the tidal volume

( $E_{rs} = \frac{P_{plat} - PEEP}{V_T}$ ). Finally, the pleural pressure is then estimated by calculating the fraction of airway pressure that distends the chest wall and thus is transmitted to the pleural

space,  $P_{pl} = P_{ao} * (\frac{E_{cw}}{E_{rs}})$ . Assuming the influence of the mediastinum is constant throughout the respiratory cycle, no correction factor would be necessary. (23) However, an important assumption with the elastance-derived method is that  $P_{pl}$  is 0 when airway pressure is 0, which is seldom true. If true pleural pressure is higher or lower than 0 when airway pressure equals 0, the calculated pleural pressures with this technique will be under- or over-estimated, respectively. It should also be noted that the elastance-derived calculation measures expiratory  $P_{es}$  at PEEP rather than atmospheric pressure and assumes that changes in esophageal and airway pressure are linear during tidal ventilation or with changes in PEEP. (6) A recent study addressed this by measuring  $P_{es}$  with esophageal manometry when airway pressure was zero by disconnecting patients from ventilators and allowing them to exhale to atmospheric pressure. (24) The elastance-derived  $P_{TP}$  had excellent correlation with that technique and does not require the patient to be disconnected from the ventilator. The investigators concluded that the elastance derived  $P_{TP}$  could be used as a proxy for end-inspiratory stress with mechanical ventilation. (24)

Further assumptions must also be made with either calculation technique regarding the generalizability of the measured  $P_{es}$  to the surface pleural pressures surrounding the entire lung. Pelosi et al demonstrated that  $P_{es}$  accurately estimated pleural pressure in the middle lung zone in a canine model of ARDS. (25) However,  $P_{es}$  also overestimated pleural pressure in the nondependent regions of lung and underestimated it in the dependent regions of the lung. (25) In addition to the gravitational pleural pressure gradient, there may also be local variations of pleural pressure related to the resistance to parenchymal shape deformation in consolidated lung. (26, 27) Left lower lobe atelectasis is common in supine patients, presumably from localized increases in pleural pressure, and the esophageal catheter is typically in position closest to the left lower lobe. For these reasons,  $P_{es}$  may be an accurate surrogate for pleural pressure in a localized area of the lung but may not be a good representation for much of the aerated lung in other regions. In this fashion, using  $P_{TP}$  to set PEEP or tidal volume may prevent lung collapse or promote recruitment in the area of the esophageal catheter, but it may actually promote derecruitment or overdistention injury in other areas of lung. The location of VILI may be shifted but not necessarily reduced.

## $P_{TP}$ -guided Mechanical Ventilation

Despite these caveats, several studies have used  $P_{TP}$  to adjust mechanical ventilation in patients with lung injury. In a small cohort of patients with severe H1N1-associated ARDS referred for ECMO, clinicians increased PEEP until the end-inspiratory  $P_{TP}$  was 25 cm H<sub>2</sub>O, using the elastance method.(13) Approximately half of the patients substantially improved their arterial oxygenation and could then be managed with conventional ventilation without ECMO. Similar to the “open lung approach”(28), this strategy focuses on promoting lung recruitment while limiting overdistention injury by monitoring end-inspiratory lung stress. It is unclear, however, if it addresses the potential for VILI during expiration, as end-expiratory  $P_{TP}$  is not evaluated.

Talmor and colleagues noted that the directly calculated  $P_{TP}$  at end-expiration was often negative in patients with ARDS, suggesting that airway closure or flooding had prevented alveolar pressure from equilibrating with airway pressure.(29-31) Therefore, they suggested that PEEP should be adjusted to maintain a positive end-expiratory  $P_{TP}$  to keep airways open at end-expiration, prevent derecruitment, and thus lower the risk of VILI.(31) They utilized the direct calculation method ( $P_{TP} = P_{ao} - P_{es}$ ) to guide PEEP levels in 61 ARDS patients. (29-31) Patients were randomized to either a control group in which PEEP was set using the NIH ARDS Network PEEP/FiO<sub>2</sub> table(5) or an experimental group in which PEEP was titrated to an end-expiratory  $P_{TP}$  of 0-10 cm H<sub>2</sub>O while maintaining end-inspiratory  $P_{TP}$  less than 25 cm H<sub>2</sub>O.(30) The study was terminated early after interim analyses demonstrated substantial improvements in the primary outcome of arterial oxygenation. It is not surprising that the higher PEEP levels used in the intervention group (18 vs 12 cm H<sub>2</sub>O) would lead to improved oxygenation, but there were also significant gains in respiratory system compliance, suggesting that there was greater lung recruitment in the group managed by  $P_{TP}$ . The trial was not powered to compare mortality between the two groups, but there was a trend towards lower 28-day mortality in the  $P_{TP}$ -guided group.(30) The same research group is now conducting a larger randomized trial in moderate-to-severe ARDS patients, comparing  $P_{TP}$ -guided PEEP titration to a uniform higher PEEP strategy, with primary outcomes of ventilator free days and mortality.(32) Until results from further clinical trials demonstrate significant improvements in survival using  $P_{TP}$  guided mechanical ventilation, there will continue to be reservations regarding its general applicability to this heterogeneous population.

Even when esophageal catheters are used to estimate  $P_{pl}$ , there remains substantial heterogeneity regarding the best method for calculating  $P_{TP}$  and setting PEEP. As described, one approach utilizes directly calculated  $P_{TP}$  to adjust PEEP to maintain end-expiratory  $P_{TP} > 0$  cm H<sub>2</sub>O.(30) The other utilizes elastance-derived  $P_{TP}$  to target an end-inspiratory  $P_{TP}$  equal to 25 cm H<sub>2</sub>O.(13) It is not surprising that when both strategies were applied to the same patients, they yielded very different PEEP values.(33) Moreover, in a third of the patients the two approaches recommended PEEP changes in opposite directions.

The PEEP settings recommended by these methods have not always had face validity. Most clinicians would expect that the optimal approach to setting PEEP would bear some relationship to ARDS severity or lung recruitability. For example, it would provide higher

levels of PEEP to patients with more potential for lung recruitment, often those patients with more severe ARDS. It would also provide lower levels of PEEP in patients with less severe ARDS who might only suffer overdistention injury with higher pressures. However, in a recent study of 51 ARDS patients, the PEEP levels that resulted from targeting positive end-expiratory  $P_{TP}$  were similar for all patients regardless of the severity of their ARDS and were unrelated to lung recruitability as measured by CT scan.(34)

One study suggested that minimizing the changes in  $P_{TP}$  during tidal ventilation (transpulmonary driving pressure,  $P_{TP,insp} - P_{TP,exp}$ ) may be a more appropriate strategy to balance between overdistention and lung recruitment. In an animal model, ventilator strategies designed to maintain low transpulmonary driving pressure also minimized lung inflammatory markers, type I epithelial cell damage, and pulmonary mechanical stress compared to high transpulmonary driving pressure models.(35) Recently, though, Marini and colleagues demonstrated in a large animal model of bilateral lung injury that airway driving pressure ( $P_{plateau,insp} - PEEP$ ) parallels transpulmonary driving pressure. This relationship held as intraabdominal pressure was varied, although it was less reliable in normal or unilaterally-injured lungs. (36)

## Other Methods for Avoiding VILI

The most intriguing aspect of utilizing  $P_{TP}$  in ARDS remains its potential to individualize ventilator settings to each patient's lung mechanics to minimize the risk of VILI. Unfortunately, esophageal manometry is laden with potentially inaccurate assumptions and correction factors. There are alternatives, however, which may allow PEEP to be individually optimized without requiring the measurement of  $P_{es}$ .

For example, one small study of 11 ARDS patients found that the recommended PEEP level to maintain a positive  $P_{TP}$  was not significantly different from the PEEP level that achieved maximal respiratory system compliance as measured with a decremental PEEP titration.(37) Another study suggested that calculation of the stress index was better than either plateau pressure or  $P_{TP}$  for preventing overdistention injury.(38) Stress index is a characteristic of the airway pressure-time relationship during tidal ventilation that reflects the balance between alveolar overdistention and cyclic recruitment-derecruitment. In a similar fashion, airway driving pressure at a constant tidal volume reflects the tidal compliance of the respiratory system and may represent the potential for VILI from these same mechanisms. Based on a recent analysis by Amato and colleagues, airway driving pressure appears to be a critical mediator of VILI and a strong predictor of mortality.(39) Further prospective trials, however, must be conducted using airway driving pressure to guide ventilator management before it can replace more established methods for adjusting ventilator settings.

## Conclusion

There is growing interest in personalizing ventilator interventions to each patient based on physiological principles to ameliorate VILI. The use of  $P_{TP}$  to achieve this type of precision medicine is inherently appealing, and esophageal manometry offers a plausible technique for estimating  $P_{TP}$ .(40) Some trials utilizing  $P_{TP}$  to adjust ventilator settings have shown



encouraging results for improving arterial oxygenation and possibly mortality.(13, 30) However, other studies suggest optimal PEEP or tidal volume in ARDS may be achieved through less invasive means than  $P_{TP}$  monitoring, fraught with fewer technical errors and assumptions, such as respiratory system compliance, stress index, oxygenation tables, or airway driving pressure. More research is needed to determine the best strategies for PEEP and tidal volume titration in ARDS.

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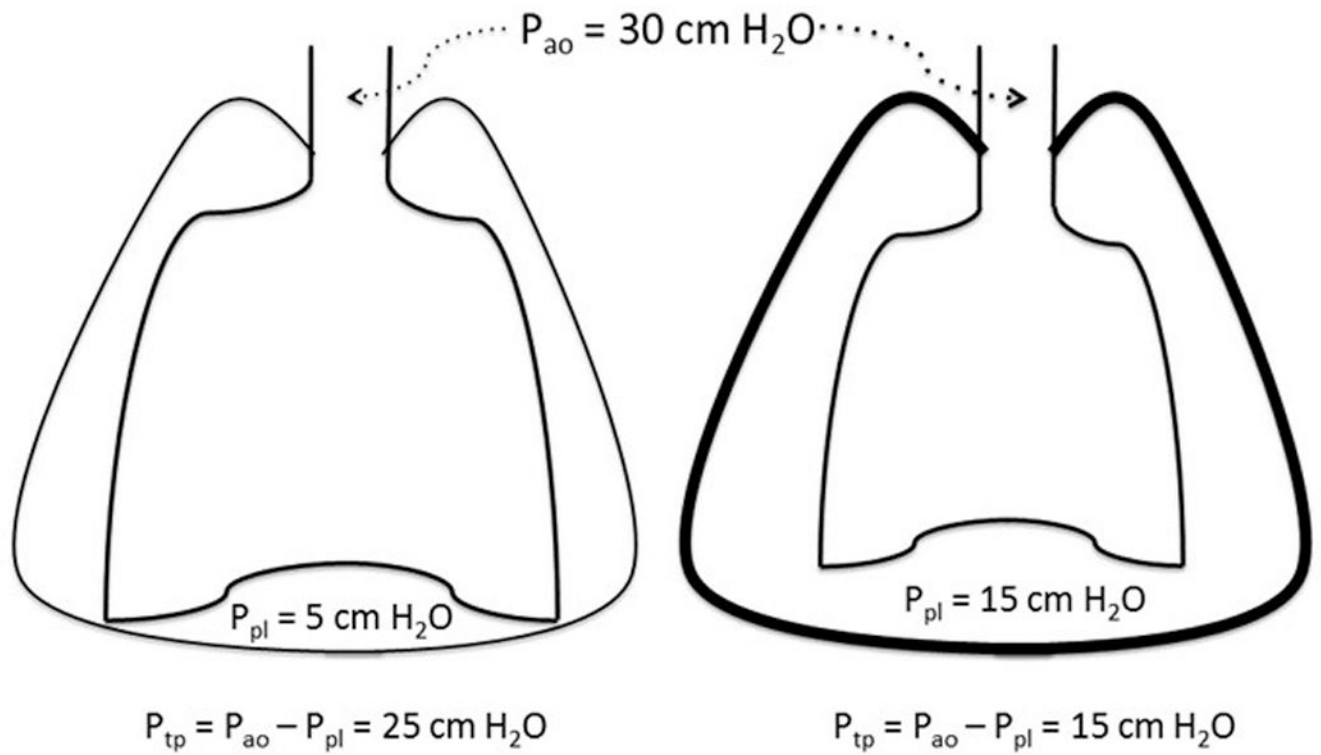


publication of the methods being used in a trial that will compare P<sub>TP</sub>-guided PEEP management with an uniform high PEEP strategy for patients with moderate to severe ARDS. The trial is currently enrolling and primary outcomes will include mortality and ventilator free days.

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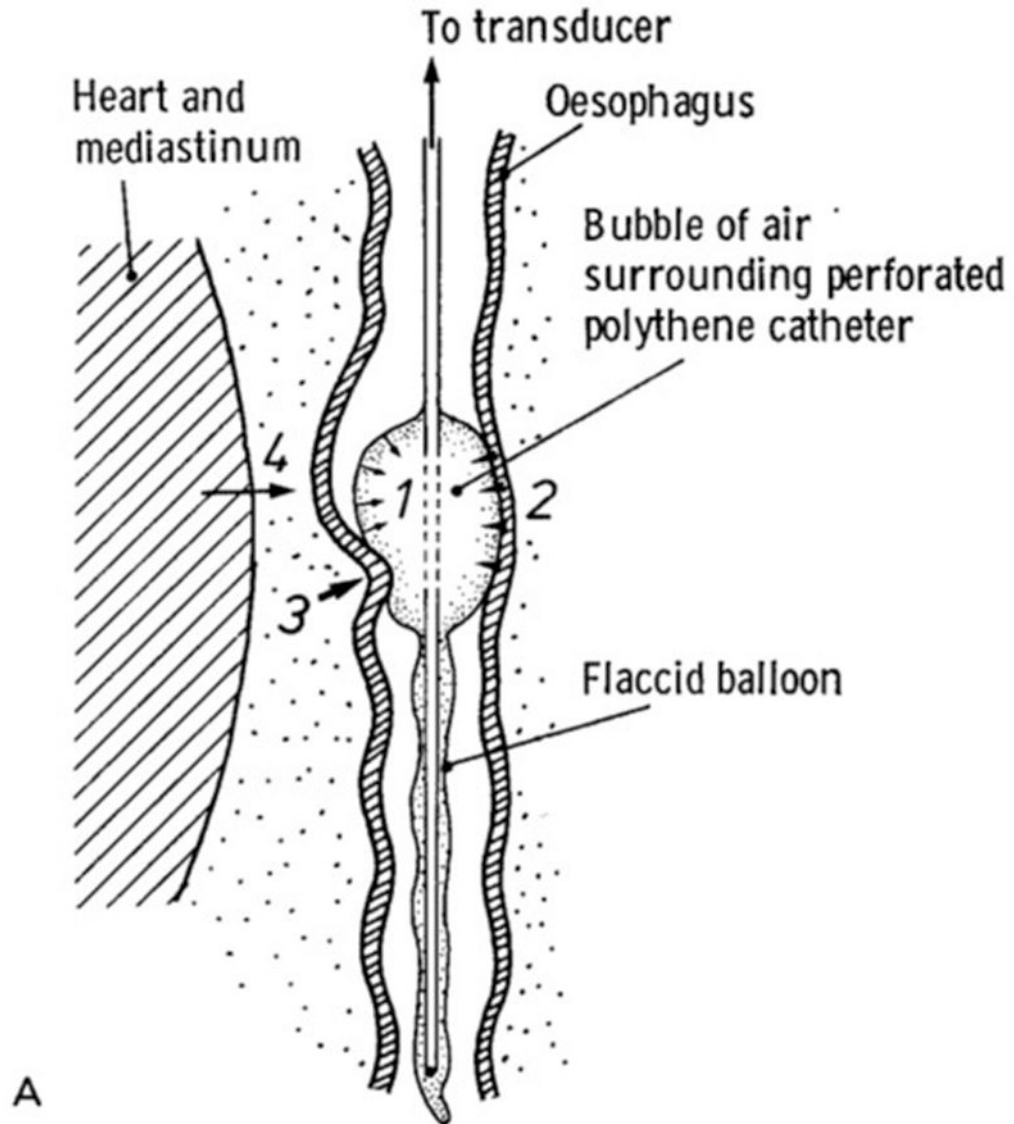
### Key Points

- Airway pressure alone may be misleading for the assessment of ventilator induced lung injury in ARDS.
- Transpulmonary pressure might provide a more accurate assessment of stress in the lung parenchyma and allow for the customization of ventilator settings to individual lung mechanics.
- The measurement of transpulmonary pressure requires the estimation of pleural pressure from esophageal manometry, which may be limited by several assumptions and potential sources of error.
- Use of transpulmonary pressure to guide PEEP selection led to improved arterial oxygenation and respiratory system compliance in clinical trials.
- Alternative less invasive methods may provide comparable options for optimizing PEEP or tidal volume in patients with ARDS.



**Figure 1.**

Airway pressure alone can be misleading. The same measured airway pressure can be associated with different transpulmonary pressures depending on the individual pleural pressures. These different transpulmonary pressures represent different levels of stress in the lung parenchyma which would be misinterpreted if only airway pressure is evaluated.



**Figure 2.** Sources of error in pleural pressure estimation by esophageal manometry. Esophageal Pressure may be affected by a) elastic recoil of the balloon; b) elastic recoil of the esophagus; c) active esophageal contractions; or d) transmitted pressure from surrounding structures. Reprinted with permission from Elsevier. (17)