Are Esophageal Pressure Measurements Important in Clinical Decision-Making in Mechanically Ventilated Patients?

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Low-tidal-volume ventilation strategies are clearly beneficial in patients with acute lung injury and acute respiratory distress syndrome, but the optimal level of applied positive end-expiratory pressure (PEEP) is uncertain. In patients with high pleural pressure on conventional ventilator settings, under-inflation may lead to atelectasis, hypoxemia, and exacerbation of lung injury through "atelectrauma." In such patients, raising PEEP to maintain a positive transpulmonary pressure might improve aeration and oxygenation without causing over-distention. Conversely, in patients with low pleural pressure, maintaining a low PEEP would keep transpulmonary pressure low, avoiding over-distention and consequent "volutrauma." Thus, the currently recommended strategy of setting PEEP without regard to transpulmonary pressure is predicted to benefit some patients while harming others. Recently the use of esophageal manometry to identify the optimal ventilator settings, avoiding both under-inflation and over-inflation, was proposed. This method shows promise but awaits larger clinical trials to assess its impact on clinical outcomes. *Key words. esophageal manometry; mechanical ventilation; acute lung injury; ALI; acute respiratory distress syndrome; ARDS; positive end-expiratory pressure; PEEP; pleural pressure; transpulmonary pressure.* [Respir Care 2010; 55(2):162–172. © 2010 Daedalus Enterprises]

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Introduction

Esophageal pressure (P_{es}) has been measured in man for over 50 years.[1,2] More recently it has been proposed as a surrogate for pleural pressure. This would allow the calculation of transpulmonary pressure and provide a means to guide the management of mechanically ventilated patients. Although it has been used to measure work of breathing and to guide weaning,[3] we will limit our comments to the management of acute respiratory distress syndrome (ARDS) and acute lung injury (ALI). Improvements in ventilator management have reduced the high mortality and morbidity associated with ARDS. It is known from decades of animal experimentation that mechanical ventilation can cause ventilator-induced lung injury (VILI) from lung over-distention at end-inspiration, and from repetitive airway opening and closing.[4]

VILI can be reduced by limiting tidal volume (V_T) and end-inspiratory plateau pressure (P_{plat}), which reduces ARDS mortality.[5] Consequently, small V_T and lower P_{plat} have become the standard of care for such patients. During spontaneous inspiration to total lung capacity, transpulmonary pressure (airway pressure [P_{aw}] minus pleural pressure) is approximately 25–30 cm H_2O, which corresponds to a P_{plat} of 30–35 cm H_2O in a patient with normal chest wall compliance. Animal studies showed little lung inflammation or injury when mechanical ventilation of normal lungs remained below 30–35 cm H_2O.[6] Although ALI and ARDS lungs are mechanically heterogeneous, restricting P_{plat} to < 30–35 cm H_2O avoids injurious over-distention of even the most normal regions.[7-9]

Attempts have also been made to mitigate the injurious effects of repetitive airway opening and closure by manipulating PEEP. Higher PEEP prevents lung regions from closing during expiration and allows ventilation of other lung regions that might otherwise remain atelectatic throughout the respiratory cycle. Unfortunately, several large randomized clinical trials found no survival advantage from managing ARDS with higher PEEP.[10-12] Several explanations have been suggested for that disappointing result. Unless accompanied by further V_T reduction, higher PEEP may increase lung stretch at peak inspiration, so one source of injury may be traded for another. In addition, the response to increased PEEP is heterogeneous. Some individuals effectively recruit lung, whereas others may over-distend lung that was already recruited. The best way to set PEEP, to optimally balance recruitment and distention in each patient, remains elusive.

Based on these concepts, the use of P_{es} to set PEEP is hypothetically very attractive. P_{es} is often quite elevated in patients with ARDS. Thoracic-wall compliance may be reduced and P_{es} elevated due to body habitus, abdominal distention, edema, or other mechanical abnormalities. The calculated transpulmonary pressure is often a negative value at end-expiration.[13] This is presumed to reflect closed airways. In the presence of closed airways and flooded or atelectatic lung, the P_{aw} measured proximally (the set PEEP) may underestimate alveolar pressure, resulting in a negative calculated transpulmonary pressure. Raising PEEP until transpulmonary pressure becomes positive at end-expiration could assure that airways remain open. Furthermore, the same chest wall factors that elevate P_{es} at end-expiration also elevate P_{es} at end-inspiration. P_{plat} may reach 35 cm H_2O or more when transpulmonary pressure is in fact much lower than it would be in a patient with normal chest wall mechanics. Measuring P_{es} and calculating transpulmonary pressure directly would allow PEEP to be increased while assuring that transpulmonary pressure at end-inspiration still remains in a safe range.

As theoretically appealing as this approach may be, evidence for its effectiveness is only beginning to emerge. There are concerns about the accuracy of P_{es} measurements in patients with ALI/ARDS, and the relevance of the P_{es} as a reflection of the relevant pressure on the pleura surface. Ventilator management using P_{es} measurement to set PEEP while limiting peak transpulmonary pressure improves oxygenation.[14] We will review the concepts and data supporting and refuting this approach.

Pro: Esophageal Pressure Measurements Are Important in Clinical Decision Making in Mechanically Ventilated Patients

Pleural and Transpulmonary Pressures During Mechanical Ventilation

Clinicians manage mechanical ventilation to prevent VILI by monitoring and controlling airway pressures. For example, PEEP is set to control P_{aw} at end-expiration, and end-inspiratory P_{plat} is monitored to minimize the risk of over-distention. This is a reasonable strategy to the extent that pleural pressure is predictable or restricted to a narrow range, but pleural pressure ranges widely and unpredictably in patients with ARDS, due to factors such as obesity and abdominal fluid accumulation, which influence the mechanical behavior of the chest wall. A wide pleural pressure range among individuals could affect the lung inflation produced by mechanical ventilation. For example, a seemingly high PEEP of 18 cm H_2O could still be too low in a patient with a pleural pressure of 20 cm H_2O, allowing repetitive collapse of air spaces with each expiration, or it could be too high in a patient with a pleural pressure of 5 cm H_2O, over-distending the lungs at end-inflation. Because P_{aw} reflects the sum of pressures across the lung and chest wall, the portion of the applied pressure inflating the lung (transpulmonary pressure) could vary widely, depending on chest wall characteristics.[15]

One cause of elevated pleural pressure is obesity, which is known to cause restrictive chest wall physiology and low lung volumes indicative of high pleural pressure. More commonly, elevated pleural pressure can result from resuscitation with large fluid volumes and the resulting edema of the intrathoracic and intra-abdominal tissues. In pigs, Mutoh and colleagues found that intravascular volume infusion produced abdominal distention, lung volume restriction, chest wall stiffening, increased pleural pressure, and decreased chest wall and lung compliance.[16] Similar effects were produced by increasing the intra-abdominal pressure by inflating an abdominal balloon. Malbrain et al estimated the prevalence of intra-abdominal hypertension from bladder pressure in 97 critically ill patients admitted to medical and surgical intensive care units.[17] Bladder pressure, which approximates intra-abdominal pressure,[18] was normal in only 41% of patients, whereas 58% of the patients had intra-abdominal hypertension, defined as bladder pressure of 16–27 cm H_2O. Eight percent of the subjects had bladder pressure over 27 cm H_2O, indicating abdominal compartment syndrome. In passively ventilated patients, intra-abdominal pressure is transmitted to the pleural space, so these findings suggest that pleural pressure also differs widely among such patients. The abdominal pressure range in these patients spans nearly the entire range of PEEP values that would ordinarily be used for mechanical ventilation in ALI/ARDS.

Although the first successful trial of low-V_T ventilation for ALI/ARDS used high PEEP,[19] and a later trial found that lung-protective ventilation with higher PEEP reduces the release of pro-inflammatory cytokines,[20] subsequent trials have not confirmed a survival benefit from higher PEEP,[10-12,21] and the protective role of PEEP in preventing VILI remains in doubt.[22] Why is it that higher PEEP, which was protective in numerous animal experiments, has been of equivocal benefit in clinical trials of ventilator strategies for ALI/ARDS? One possible explanation is that the end-inspiratory P_{plat} and PEEP specified in the clinical protocols do not reflect transpulmonary pressure, the actual inflating pressure of the lung. Estimating pleural pressure to calculate transpulmonary pressure may allow better control of both end-inspiratory and end-expiratory lung volume, and thereby reduce VILI caused by over-distention or atelectrauma.

Esophageal Pressure as a Surrogate for Pleural Pressure

It is not feasible to directly measure pleural pressure in humans. However, pleural pressure has long been estimated in upright subjects by measuring P_{es} with a balloon-tipped catheter. It is well accepted that the respiratory changes in P_{es} are representative of changes in pleural pressure applied to the lung surface.[23] Furthermore, P_{es} is considered representative of an effective pleural pressure surrounding the lung, such that the difference between P_{aw} and P_{es} is a valid estimate of transpulmonary pressure.[23]

By contrast, in mechanically ventilated supine patients with ALI/ARDS, P_{es} is rarely used to estimate pleural pressure. Although several investigators have reported the changes in P_{es} with changes in lung volume to characterize lung compliance, they did not report the baseline value of P_{es}. There are several reasons why baseline P_{es} values in mechanically ventilated patients are often ignored. First, studies in normal subjects have shown that P_{es} at a given lung volume is higher in the supine position than in the upright posture.[1,2,24,25] Lung compliance also appears to be reduced in the supine position,[2,24-26] a finding attributed to compression of the esophagus by the mediastinal contents.[1,2,25,26] Lesser changes in P_{es} have been observed upon changing from supine to prone or lateral positions.[1,25] These postural effects complicate the interpretation of P_{es} even in healthy subjects, when supine.

The properly positioned esophageal balloon catheter sits at approximately the midpoint of the lung's gravitational plane in both the upright and supine positions. In the normal individual, the P_{es} therefore reflects pressure at mid-lung height, somewhat underestimating pressure surrounding the dependent lung and overestimating that surrounding the non-dependent lung. In ALI/ARDS the lung tissue is more dense, increasing the gravitational gradient in pleural pressure.[27] Thus, the mid-thoracic P_{es} may differ more from the pleural pressure in the most dependent and non-dependent lung regions. Furthermore, diseased lungs are often mechanically inhomogeneous and less deformable, increasing inter-regional differences in pleural pressure due to shape change.[28] These considerations have led to a widespread assumption that P_{es} is not a useful measure of lung surface pressure in such patients, and that it should not be used to estimate transpulmonary pressure.[28] However, this hypothesis has not actually been tested. To the contrary, in a canine model of ARDS, Pelosi et al[29] demonstrated that the actual value of P_{es} accurately estimated the pleural pressure within the mid-lung zone (Fig. 1). Optimizing mechanical ventilation to transpulmonary pressure in this mid-lung region may be a more appropriate strategy than one that relies on measurement of P_{aw} alone. Moreover, optimizing inflating pressures to the mid-lung may prevent over-distention of the upper, non-dependent portions of aerated lung while preventing collapse of the lower, dependent portions.

Concern has been raised that artifacts induced by the mediastinal contents make P_{es} an unreliable estimate of pleural pressure in supine patients with ALI.[28] Washko et al characterized the magnitude and variability of pos-
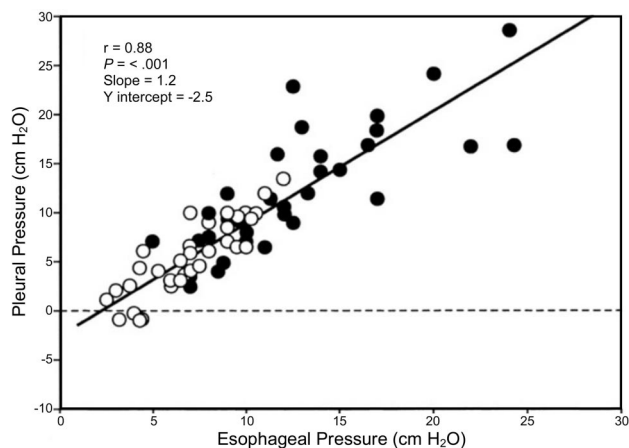
Fig. 1. Relationship between esophageal pressure and pressure directly measured in the pleural space in the mid-lung area. This indicates an excellent correlation. (Adapted from Reference 30, with permission.)
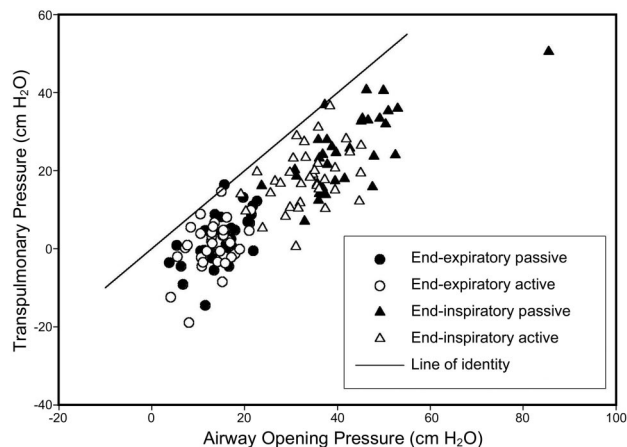

Fig. 2. The relationship between estimated transpulmonary pressure and pressure at the airway opening. The transpulmonary pressure significantly correlates with airway-opening pressure both at end-expiration ($r^2 = 0.24$, $P < .001$) and end-inspiration ($r^2 = 0.45$, $P < .001$). There was, however, consistent underestimation of transpulmonary pressure, as evidenced by the offset from the line of identity. The transpulmonary pressure at end-inflation was higher in passively ventilated subjects than in those making active respiratory efforts, possibly because sicker patients with stiffer lungs were more likely to be deeply sedated or paralyzed, and thus passive. (Adapted from Reference 13, with permission.)

tural effects on P_{es} in 10 healthy subjects.[24] They measured the position-related changes in relaxation volume and total lung capacity in healthy subjects in 4 postures: upright, supine, prone, and left-lateral decubitus. They also measured static pressure-volume characteristics of the lung over a wide range of lung volumes in each posture, with an esophageal balloon-catheter. Transpulmonary pressure at relaxed functional residual capacity (FRC) averaged 3.7 ± 2.0 cm H_2O upright and -3.3 ± 3.2 cm H_2O supine. Approximately 58% of the decrease in relaxed transpulmonary pressure between the upright and supine postures was due to the associated decrease in lung volume. The remaining 2.9 cm H_2O difference was attributed to the weight of the mediastinal contents, and is consistent with reported values of a presumed postural artifact. Washko et al concluded that adding a 3 cm H_2O correction to the transpulmonary pressure value calculated with P_{es} would account for the effects of lying supine. These data provide validation for the concept that P_{es} can be used to estimate pleural pressure in supine subjects.

In a subsequent observational study with patients with ALI/ARDS, P_{es} averaged 17.5 ± 5.7 cm H_2O at end-expiration and 21.2 ± 7.7 cm H_2O at end-inflation, and did not correlate with body mass index or chest wall elastance. Note that these values are much greater than the small artifact of added mediastinal weight. Estimated transpulmonary pressure was 1.5 ± 6.3 cm H_2O at end-expiration, 21.4 ± 9.3 cm H_2O at end-inflation, and 18.4 ± 10.2 cm H_2O during a static end-inspiratory hold. Interestingly, in many patients the end-expiratory transpulmonary pressure calculated with P_{es} was a negative number, suggesting that substantial numbers of ventilated patients may have cyclic collapse of lung units at

end-expiration when ventilated with standard settings (Fig. 2).[13]

It could be argued that limiting V_T would consistently limit transpulmonary pressure and prevent over-distention, but data from that same study showed no correlation between V_T and transpulmonary pressure at end-inspiration. Taken together, these data suggest that both P_{aw} and V_T may be inadequate surrogates for transpulmonary pressure during mechanical ventilation, and that actual measurement of P_{es} is required to calculate transpulmonary pressure.

Based on these observations it has been postulated that P_{es}, corrected for positional variation, as described by Washko and colleagues, reflects an effective pleural pressure in critically ill patients as accurately as it does in healthy individuals. Furthermore, P_{es} can be used to estimate the transpulmonary pressure during static maneuvers, as a guide to setting PEEP. Appropriate PEEP would prevent derecruitment and thus lower the risk of VILI.[13,24] Despite the caution by Pelosi et al that P_{es} does not always exactly agree with the directly measured pleural pressure,[30] consistent trends in transpulmonary pressure estimated from P_{es} have now been reported by Pelosi et al[30] and Talmor et al.[13] Those data provide evidence of the highly variable and unpredictable pleural pressure in ALI/ARDS and provide a rationale for modifying ventilation settings based on physiologic measurements.
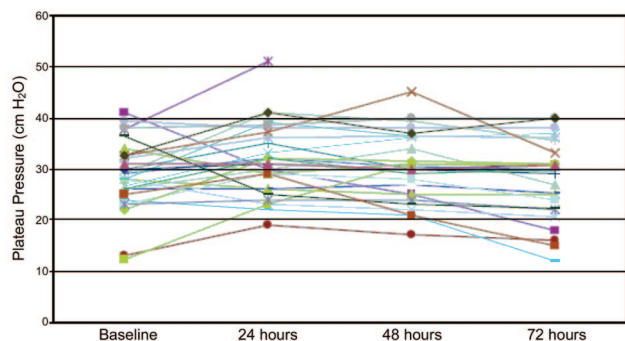
Fig. 3. Plateau pressure in patients who had positive end-expiratory pressure set based on esophageal pressure measurements. Many patients had potentially injurious plateau pressure. (Adapted from Reference 14, online supplementary Appendix 2, with permission.)
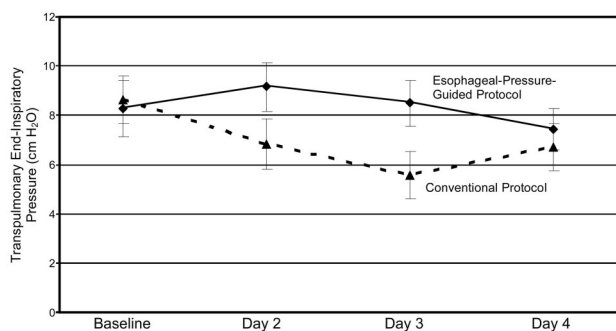

Fig. 4. Transpulmonary end-inspiratory pressure at baseline, day 2, day 3, and day 4 in a study that compared a conventional mechanical ventilation strategy to a strategy guided by esophageal pressure measurements.[14] Conventional protocol compared to esophageal-pressure-guided protocol by repeated measures. At no point did the transpulmonary pressure at end-inspiration approach an excessive value. (Adapted from Reference 14, with permission.)

Clinical Observations Using Esophageal Pressure

A phase-2 randomized controlled trial of mechanical ventilation directed by P_{es}, compared to ventilation based on the ARDS Network protocol,[14] used oxygenation as the primary outcome and was terminated early because of overwhelming effect, after enrolling 61 patients. There were no unexpected study-related adverse events in either group. The ratio of P_{aO_2} to fraction of inspired oxygen (F_{IO_2}) at 72 hours was 88 mm Hg higher in the intervention group (95% CI 78.1–98.3, $P = .002$), and this improvement was evident at 24, 48, and 72 hours ($P = .001$ via repeated-measures analysis). Respiratory-system compliance was also significantly improved in the intervention group ($P = .002$ via repeated-measures analysis at 24, 48, and 72 h). In the intervention group there was also a trend toward lower 28-day and 6-month mortality.[13] Though P_{plat} was elevated in the intervention group ($P = .003$ via repeated-measures analysis) (Fig. 3), it was generally < 30 cm H_2O. Though that P_{plat} is generally considered "safe," remember that the ARDS Network has published data that suggest that in fact no P_{plat} is really "safe."[31] transpulmonary pressure during end-inspiratory occlusion never exceeded 24 cm H_2O and was not significantly different between the groups ($P = .13$ via repeated-measures analysis) (Fig. 4). This transpulmonary pressure more accurately reflects the distending pressure in the lung.

These preliminary investigations suggest that a ventilation strategy designed to optimize transpulmonary pressure is feasible and may be superior to ventilation based on the ARDS Network protocol, which is the current standard of care. Though further validation in larger studies with more clinically relevant outcomes is required, these data showing improved lung mechanics and gas exchange and the possibility of lower mortality in ARDS provide a compelling rationale for the routine use of esophageal manometry in clinical decision making in these patients.

Con: Esophageal Pressure Measurements Have Not Been Shown to Be Important in Clinical Decision Making in Mechanically Ventilated Patients

The use of esophageal manometry to guide clinical decisions in mechanically ventilated ALI/ARDS patients is at best premature and at worst dangerously misleading. By way of analogy, for decades the measurements obtained via pulmonary artery catheter were deemed essential for clinical decision making in a great many critically ill patients. This presumed importance was founded in the incontestable logic of the underlying physiologic principles, and was supported by the widespread belief that similar information was unavailable by other means. The eminence of the pulmonary artery catheter collapsed when the accuracy of the data, the legitimacy of the decisions based on those data, and their effect on patient outcomes were subjected to careful scrutiny. The edifice of the pulmonary artery catheter turned out to be artifice.

For information to be important in clinical decision making it must do more than merely direct a clinical decision. It must provide information that is not available by simpler means, and it should direct a decision that improves important patient outcomes. One must first establish whether P_{es} accurately represents pleural pressure in critically ill patients. If the measured pressure does not represent the physiologic variable for which it is a surrogate, then any decisions based on it are suspect. Like the pulmonary artery catheter, the measurement of P_{es} is physiologically appealing but clinically unrevealing. The reasons are similar: to be accurate, the measurement must be made with great attention to detail, the interpretation is generally overly simplistic, and the decisions based on the P_{es} measurement have no impact on important outcomes. Furthermore, as with the pulmonary artery catheter, much of the informa-

tion sought by measurement of P_{es} can be inferred from other, less invasive means. In the case of setting PEEP in mechanically ventilated ALI/ARDS patients, the decisions directed by using P_{es} appear to be diametrically opposite to those directed by other physiologic data.

Esophageal Pressure Measurement: Sources of Error

P_{es} measurement technique was studied in detail in the 1950s and 1960s, when measurements were being applied to studies of normal lung mechanics. Open-ended catheters, filled with either fluid or air, are unsuitable, because the surface forces at air-fluid interfaces within the esophagus or catheter distort the measured pressure. Because the radii of curvature at these interfaces are small and the fluid generally has high surface tension, the errors can be substantial when small pressures are being measured.

To avoid these surface force errors, P_{es} is measured with an air-filled catheter terminating in a thin balloon. The standard balloon is 10 cm long, and the catheter has multiple side holes within the balloon. If the balloon contains a volume below its unstressed volume, it will have no pressure gradient across its wall, so the pressure within the balloon will equal the pressure within the esophagus. With too little air volume the positive pressure in the esophagus will compress the remaining gas and empty the balloon. The measured pressure will then underestimate the P_{es}. Too much air volume will distend the local region of the esophagus, or even the balloon, and the measured pressure will overestimate the pressure in the empty esophagus.

The technique has been standardized as follows. After the balloon-tipped catheter is positioned (see below), it is opened to the air while the subject bears down to raise pleural pressure and empty the balloon. The subject relaxes, 5 mL of air are injected into the balloon, and 4.5 mL are removed. This ensures that the balloon is not twisted around the catheter and compartmentalized, and leaves a volume of air that will minimally distort the measured P_{es}. The residual bubble will flow to wherever the pressure within the balloon is lowest.[1]

Pressure within the esophagus varies considerably between the gastroesophageal junction and the thoracic inlet.[1] Some of this reflects the hydrostatic gradient of pleural pressure from non-dependent to dependent regions. However, much of the variability of P_{es} is due to local differences in P_{es}, which are unrelated to the pleural pressure. They are therefore considered artifacts, which must be minimized by proper positioning of the balloon. The goal is for the P_{es} to represent the average pressure on the lung surface. Optimal positioning of the balloon has been studied by comparing the change in P_{aw} to the change in P_{es} as the subject makes gentle expulsive or inspiratory efforts against an occluded airway.[32] Since the airway is occluded, transpulmonary pressure will not change. P_{aw}

and P_{es} will not be equal (their difference is transpulmonary pressure), but they should change equally during these occluded efforts, so the ratio of ΔP_{es} to ΔP_{aw} should be near unity. This criterion is generally met in the lower third of the esophagus, approximately 10 cm above the gastroesophageal junction.[1] Note, however, that all of these investigations were performed with upright and cooperative subjects.

Furthermore, this method of optimal positioning indicates only that changes in P_{es} may accurately track changes in pleural pressure. It does not indicate that P_{es} is accurate. Changes in pressure and volume are all that are necessary to measure lung or chest wall compliance, when compliance is calculated as a slope, but an accurate P_{es} is essential to calculate a specific transpulmonary pressure.

Consider the effect of a small error in P_{es} measured at end-expiration in a normal subject (Fig. 5A). A slight overestimation of P_{es} (for example, from having a little too much air in the balloon) will cause a slight underestimation of transpulmonary pressure at any volume. This can be represented as a leftward shift of the lung pressure-volume relationship. Since the normal V_T of a normal subject occurs on a linear portion of this pressure-volume relationship, the small underestimate of transpulmonary pressure at end-expiration will be of similar magnitude at end-inspiration. But in the highly non-linear lung pressure-volume relationship in a patient with ARDS (Fig. 5B), depending on the shape and position of the lung pressure-volume relationship, a small underestimation of transpulmonary pressure at end-expiration may cause a large underestimate at end-inspiration. Stated differently, the effect of balloon volume on measured pressure is greater at high lung volume, even in normal subjects.[1] This artifact would provide false reassurance about the degree of lung distention at peak inspiration.

Another source of P_{es} error is attributable to patient positioning. Most of the seminal studies of lung mechanics have been performed in upright subjects. In the supine position the heart rests almost directly over the esophageal balloon catheter, so the measured pressure reflects the added weight of the mediastinum. In addition, FRC is lower in the supine position, which raises pleural pressure. Several studies have documented a P_{es} increase of 5–7 mm Hg upon recumbence.[2,24,25] This has been dismissed as an artifact, and the general assumption is that P_{es} cannot be used to estimate pleural pressure in supine patients. However, defining this effect as an artifact is itself somewhat artifactual. If an upright patient exhaled to a lower lung volume, pleural pressure would be higher, as defined by the pressure-volume mechanics of the thorax, so the contribution of decreased FRC in the supine position to increased P_{es} is not an artifact. Furthermore, the pressure beneath the heart in the esophagus may be similar to the pressure beneath the heart in the nearby pleural space, or
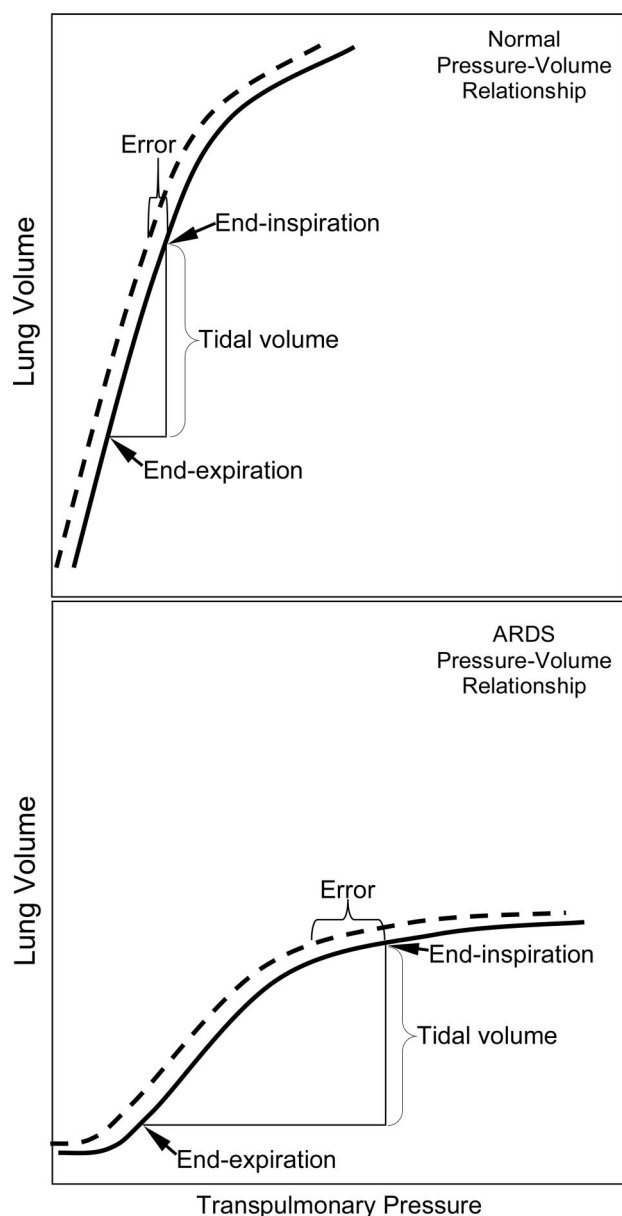
Fig. 5. Hypothetical pressure-volume relationships in the lungs of a normal subject and in a patient with acute respiratory distress syndrome (ARDS). The solid line indicates the true relationship between lung volume and transpulmonary pressure. The dashed line shows the relationship as estimated from esophageal pressure, in which esophageal pressure slightly overestimates pleural pressure. This leads to a small leftward shift of the pressure-volume relationship, and underestimation of transpulmonary pressure. Because the normal lung compliance is high and tidal breathing occurs on the linear portion of this relationship, the errors in transpulmonary pressure at end-expiration and end-inspiration are similar and small. In a patient with ARDS, lung compliance is reduced and the relationship is curvilinear. If the tidal volume ends on the more horizontal portion of the lung compliance curve, small errors in transpulmonary pressure at end-expiration can nevertheless be associated with large underestimations of transpulmonary pressure at end-inspiration. This can falsely reassure the clinician that lung over-distention is not present.

under consolidated lung that has the same density as tissue. Therefore, even in the supine position the P_{es} probably equals pleural pressure in some regions. It probably does not, however, represent an average pressure distending the lung.

Washko et al[24] performed a detailed study to quantify the P_{es} change in the supine position and to parse out the contributions of cardiac weight and decreased FRC. The difference attributable to the weight of the mediastinum was 2.9 cm H_2O, but there was substantial inter-individual variability in this cardiac artifact. The standard deviation was 2.1 cm H_2O, which means that in a third of the subjects the artifact from the weight of the mediastinum exceeded 5 cm H_2O. Thus, the ability to accurately estimate transpulmonary pressure in the supine position is quite limited, even in healthy subjects. By extension, the assumption that a given transpulmonary pressure indicates lung recruitment at end-expiration or a safe degree of lung distention at peak inspiration is limited.

The optimal positioning of the balloon catheter in the supine patient has also been questioned. Higgs et al measured the $\Delta P_{es}/\Delta P_{aw}$ in 10 anesthetized but spontaneously breathing patients without lung disease prior to surgery.[33] A short esophageal balloon was positioned 5, 10, 15, and 20 cm above the gastroesophageal junction in all the patients. The accuracy of P_{es} measurements was studied by comparing changes in P_{es} and P_{aw} during inspiratory effort with an occluded airway. Every patient had a location where the $\Delta P_{es}/\Delta P_{aw}$ was near 1, averaging 0.98 ± 0.03 in the group. However, this optimal location was not necessarily at the widely used locus 10 cm above the gastroesophageal junction. Three of the 10 patients showed large discrepancies between ΔP_{es} and ΔP_{aw} when the balloon was positioned at the standard 10 cm position: $\Delta P_{es}/\Delta P_{aw}$ was 1.2, 0.75, and 0.6 in those 3 patients at that position. Thus, the balloon positioning artifact in P_{es} may be variable and unpredictable in supine patients.

The degree to which even an accurate and artifact-free P_{es} accurately represents the generalized pressure distending the lungs has been the subject of much controversy. The pressure in the pleural space can be measured directly in animal studies. This pressure shows a gradient from non-dependent to dependent regions. In normal animals and healthy humans, this gradient is about 0.2 cm H_2O per centimeter of vertical distance.[1,34,35] It is attributable to both the pressure from overlying lung and tissue, and differences between the relaxed shape of the lung and the chest wall. In edematous, injured, and dense lungs the pleural pressure rises more steeply with dependent depth.[16]

Because P_{es} is quite high in patients with ARDS, it has been argued that the small potential errors in measurement are irrelevant, and the signal-to-noise ratio is sufficient to guide clinical measurement. However, the measurement errors have been quantified only in normal subjects. The

same characteristics that increase P_{es} in ARDS patients can also increase the error, and it would be an error of logic to assume otherwise.

The topography of pleural pressure in critically ill patients is unknown. However, when regional lung mechanics are not uniform, it is likely that regional pleural pressure is also quite variable. In animals in which expansion of one lung or lobe is prevented by bronchial occlusion, the pleural pressure change in the occluded region is less than over other lung regions during lung inflation.[36] Similar inferences have been made in non-critically-ill patients with obstructive or restrictive disease, in whom a lobe is occluded and used as a tonometer to estimate the change in pressure surrounding it when the rest of the lung is inflated.[37] Patients with ALI typically have very heterogeneous and asymmetric lung disease. Some flooded or atelectatic lung regions fail to inflate with inspiration. The range of cardiac volume encountered is much larger than normal, pleural effusions are common, and pleural fibrosis and pneumothoraces are often present. There is little rationale and no data to support the assumption that the measurement of P_{es} in such patients bears the same relationship to average pleural pressure as in upright healthy subjects. Moreover, the exaggerated change in pleural pressure with gravitational height in ARDS ensures that, in regions below the level of the esophageal balloon, the airways will have a substantially higher pleural pressure, and in regions above the balloon pleural pressure will be substantially lower. Even if PEEP were titrated to optimize lung volume at the level of the esophagus, lung regions elsewhere would be under-inflated or over-inflated.

Thus, with meticulous technique, an esophageal balloon catheter can measure the pressure in the esophagus, which in an upright normal subject represents an average pressure on the surface of the lung. In the supine normal subject the pressure is elevated to an individually variable amount by the weight of the mediastinal contents. Though it probably corresponds to the pressure at some parts of the lung surface, it may no longer reflect an average surface pressure. In critically ill patients the relationship between the measured P_{es} and the average pleural pressure is unknown. However, extrapolating from healthy subjects, it is upon that unknown relationship that clinical decisions have been based.

Using Esophageal Pressure to Guide Ventilator Management in ALI/ARDS

This approach has been tested in one study,[14] reviewed above, which found that setting PEEP based on standardized transpulmonary pressure/F_{IO_2} tables, compared to the standardized PEEP/F_{IO_2} tables used in the ARDS Network trials, led to PEEP being increased in almost all patients in that arm. As would be expected on higher PEEP, oxygen-

ation improved in the group managed with transpulmonary pressure data. Transpulmonary pressure at end-inspiration remained below a safe limit in all patients in that group. There was no significant difference in 28-day or 180-day mortality.

Because that investigation was designed to show greater improvements in oxygenation in the patients managed using transpulmonary pressure data, it concluded early as a positive study. However, this does not validate P_{es} as "important in clinical decision making." The higher PEEP used was entirely predictable, based on the prior knowledge that transpulmonary pressure would be negative at end-expiration in most patients.[13] That higher PEEP would improve oxygenation was likewise predictable from previous experience.[10-12] It remains uncertain whether lung injury was ameliorated or important outcomes improved by transpulmonary-pressure-based PEEP. About half the patients randomized to the transpulmonary-pressure group, after PEEP was adjusted, had $P_{plat} > 30$ cm H_2O. Some had $P_{plat} > 40$ cm H_2O (see Fig. 3). Since pleural pressure is heterogeneous in ARDS patients, the "safe" transpulmonary pressure in the regions near where P_{es} was measured provide no assurance that injurious overdistention was avoided in other lung regions. The best that can be concluded is that in the lung regions where P_{es} happens to have equaled pleural pressure, end-expiratory collapse and end-inspiratory over-distention may have been avoided. The improved oxygenation does not help reveal the optimal balance between recruitment and distention.

We may therefore dismiss the use of transpulmonary pressure, on the basis that it does not provide accurate information upon which to base clinical decisions, and because the decisions can be made based on simpler, less invasive methods. A protocol-based approach that individualizes PEEP based on lung recruitability was studied by Grasso et al.[38] They based their PEEP decisions on the concavity of the pressure-time plot of P_{aw} during constant-flow inflation. Those data are available on any mechanical ventilator with a graphical interface. They calculated a quantitative "stress index" from the shape of the pressure-time relationship, but the index can be interpreted qualitatively as follows: when the plot was concave up (accelerating increase in pressure as inflation proceeds), they reasoned that the lung was over-distended and PEEP should be reduced. If the plot was concave down, lung inflation was recruiting lung regions and the PEEP was safe. In 15 patients ventilated per the ARDS Network PEEP/F_{IO_2} table, they found that the majority of patients were on too much PEEP (Fig. 6). This is precisely opposite of what was suggested by the measurement of transpulmonary pressure.[14] Moreover, reducing the PEEP until the stress index
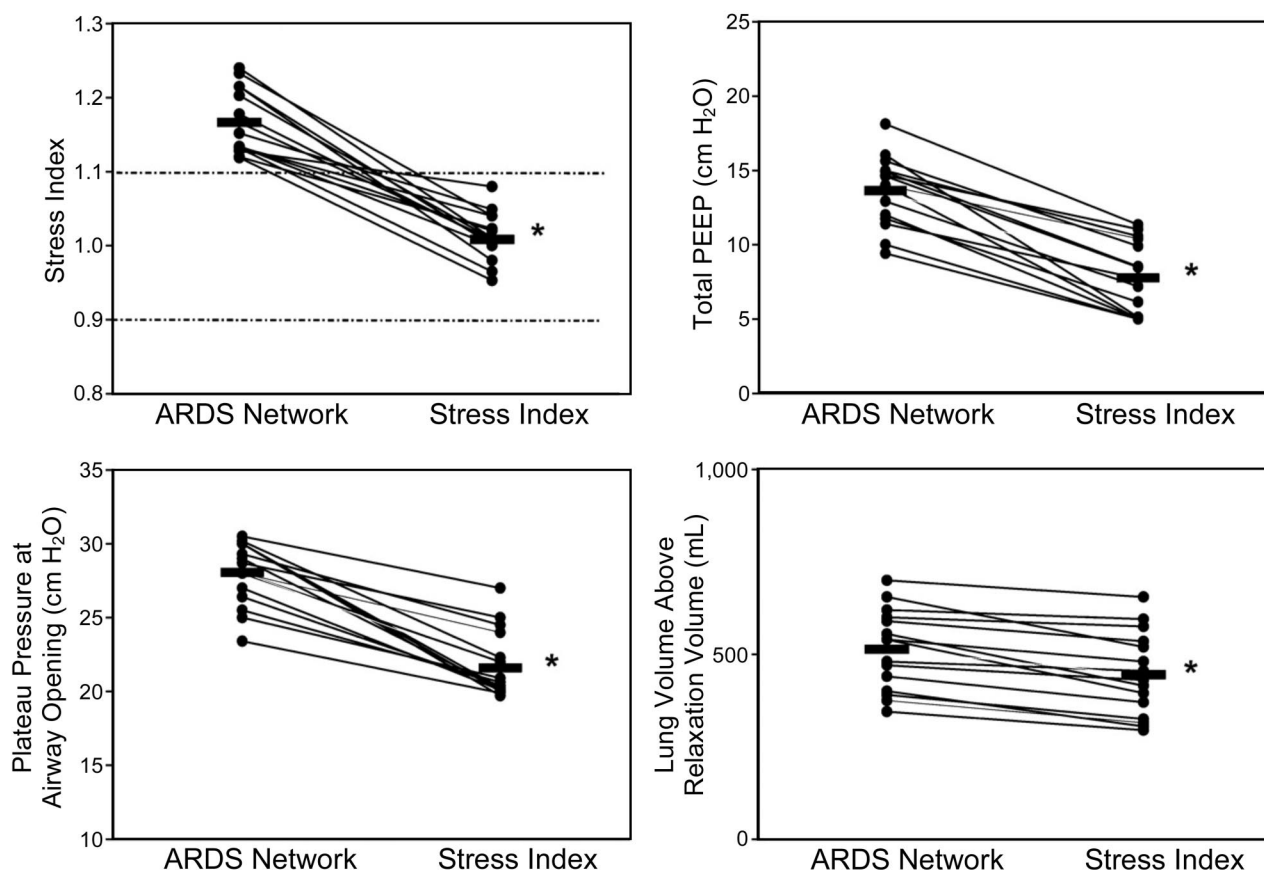
Fig. 6. Stress index, positive end-expiratory pressure (PEEP), plateau pressure, and lung volume above the elastic equilibrium volume of the respiratory system (relaxation volume), measured on the static pressure-volume curve at a pressure of 20 cm H_2O. The values on the left in each panel are those when the tidal volume, PEEP, and fraction of inspired oxygen are taken from the tables of the Acute Respiratory Distress Syndrome (ARDS) Network. The values on the right are from after PEEP has been reduced to lower the stress index to < 1.1. The inflammatory mediators interleukin 8 (IL-8), IL-6, and soluble tumor necrosis factor alpha RI were lower on the lower PEEP. (Adapted from Reference 38.)

fell below the injurious range significantly reduced inflammatory cytokines. This approach has not, however, been tested clinically.

Mercat et al compared the ARDS Network PEEP/F_{IO_2} table to individually set PEEP levels in a large multicenter trial.[12] In the intervention arm, PEEP was increased in each patient until P_{plat} was 28–30 cm H_2O, while keeping V_T near the goal of 6 mL/kg predicted body weight. Inevitably, in some of those patients P_{plat} may have reached the limit in part due to a stiff or heavy chest wall. However, using this approach, patients who recruit in response to PEEP end up on higher PEEP, while those who fail to recruit reach the P_{plat} limit at lower PEEP. The study found no difference in mortality between the 2 groups, but ventilator-free days and organ-failure-free days were greater in the higher-PEEP arm. As with the stress index, this approach can be applied without special expertise or equipment.

Thus, the assumptions upon which the use of P_{es} to set PEEP in patients with ARDS is based are flawed, and PEEP decisions can be based upon information that is simpler to obtain. Definitive data are not yet available that those PEEP decisions improve outcomes. However, sensible outcome markers (inflammatory markers and ventilator-free days) face in the right direction. Despite its conceptual appeal, P_{es} does not accurately represent the average pressure on the lung surface in supine, critically ill patients. Even if it did, the pleural surface pressures in regions above and below the esophagus would vary widely around the P_{es}. The transpulmonary pressure calculated from P_{es} would provide no assurance that VILI was being prevented in lung regions not near the esophagus. It is therefore not surprising that P_{es} fails to provide important clinical information to guide decisions about PEEP. Moreover, even if the measurements were accurate, they are unnecessary. There is no need to relive, with yet another

physiologic variable, the folly of our 30-year infatuation with the pulmonary artery catheter.

Summary

In patients with ALI/ARDS, pleural pressure in some lung regions is substantially higher than in upright normal subjects. Basing ventilator settings on a maximum allowable P_{aw} of 30–35 cm H_2O may leave large portions of the lung under-inflated and at risk of VILI from repetitive airway opening and closing. It is logical that estimating pleural pressure from P_{es} and setting PEEP to achieve a target transpulmonary pressure may allow higher PEEP in many patients without over-distending lung regions that are already recruited. However, there may also be irreducible errors in the measurement of pleural pressure in supine patients with lung disease. In addition to potential artifacts, pleural pressure varies greatly from non-dependent to dependent regions in injured lungs. Nevertheless, PEEP that yields a safe transpulmonary pressure range during tidal breathing, based on P_{es} measurements, may under-inflate or over-inflate lung regions at a distance from the esophagus. Pilot studies have shown that ventilator settings based on transpulmonary pressure generally yield higher PEEP and better oxygenation than the PEEP/F_{IO_2} tables of the ARDS Network trials. Whether that yields better clinical outcomes will have to await larger clinical trials.

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Discussion

MacIntyre: I think we have to give the Fessler/Talmor team the award for most entertaining presentations.

Dan, I was struck by Gordon Bernard's editorial[1] on your paper[2] that suggested that if you had used the high-PEEP/F_{IO_2} table from the ARDS Network's ALVEOLI [Assessment of Low Tidal Volume and Elevated End-Expiratory Volume to Obviate Lung Injury] trial,[3] you might have seen something very similar. He argued that the ALVEOLI results, which found higher P_{aO_2}/F_{IO_2} ratios, also found that plateau pressure went up, but not quite as much as the increase in PEEP, which suggested improved compliance. Is the esophageal technique you described just a more complicated way of instituting the ARDS Network high-PEEP strategy?

1. Bernard GR. PEEP guided by esophageal pressure: any added value? N Engl J Med 2008;359(20):2166-2168.
2. Talmor D, Sarge T, Malhotra A, O'Donnell CR, Ritz R, Lisbon A, et al. Mechanical ventilation guided by esophageal pressure in acute lung injury. N Engl J Med 2008;259(20):2095-2104.
3. ARDS Clinical Trials Network. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med 2004;351:327-336.

Talmor: I need to rebut Hank here. We never said that esophageal pressure reflects pleural pressure across the entire lung. The only time it's ever actually been compared, in dogs with ALI, it reflected pleural pressure in the mid-lung portion. So that clearly requires further validation, and Vilar in Spain is doing a similar validation study in humans.

As to whether the stress index gives equivalent information, well, maybe. Obtaining the stress index is not as easy as it looks in Grasso's paper.[1] He presents the very clearest tracings in his paper, but in clinical practice these are often difficult to interpret. Secondly, the stress index has never been validated in a clinical trial. There are devices on the market to measure esophageal pressure, so I am happy to tell you that Hopkins will be able to buy a few when they start using this technique.

About your question: did we just repeat the ALVEOLI high-PEEP trial? I don't think so. The PEEPs we applied were higher than those in ALVEOLI, and we titrated PEEP to the patient's individual respiratory physiology rather than basing it on a one-size-fits-all sliding scale. Now, stepping backwards, the only way we're ever going to know this is with a larger trial with multiple centers, to see how generalizable is this technique. But some pre-clinical investigation definitely needs to be done: we need a study showing some kind of imaging, and we need to validate the correlation between pleural pressure and esophageal pressure in humans. There's a lot more work to do before I'd say that esophageal pressure measurements are the way to go in ARDS. However, the question at hand is, does it add valuable information? I still believe it stands to reason that there may be valuable information here.

1. Grasso S, Stripoli T, De Michele M, Bruno F, Moschetta M, Angelelli G, et al. ARDSNet ventilatory protocol and alveolar hyperinflation: role of positive end-expiratory pressure. Am J Respir Crit Care Med Oct 15 2007;176(8):761-767.

Epstein: Let's say you do another clinical trial and it looks positive—although I would wonder about an even more aggressive PEEP strategy in the control arm, because there is a difference between what you found and what ALVEOLI and the other trials found—about a 4 cm H_2O difference in PEEP. The question is widespread application. We can't even get people to turn down the tidal volume, and now we're going to ask them to place a special catheter that requires special expertise?

What I haven't heard about is the maintenance of these catheters. I've placed hundreds of esophageal catheters in spontaneously breathing patients, but not in patients on ventilators, and the catheter is in for just a short period. These catheters move a lot, so to keep one in would require a lot of maintenance work. Is this really feasible for general clinical use?

Talmor: Let me answer that on a higher philosophical level, and then on a lower practical level. We always seem to think that we have to design our trials and our interventions for some hypothetical intensivist who doesn't have any expertise with the intervention. Most intensivists and respiratory therapists I meet are really interested in doing what's best for their patients. If we present a compelling argument, I believe they'll buy it.

At the practical level, at Beth Israel Deaconess Medical Center, I would say that, after a few years of work, more than 70% of the respiratory therapists can place the balloon and make consistent measurements. We have a great respiratory therapy director, Ray Ritz, who was integral to this trial, and he's worked hard with his people. I would say that placing an esophageal balloon and making measurements is no more difficult than placing a central line or many of the other things we do. If the clinical usefulness is proven, I believe that people will adopt the technique and use it. In a multi-center trial we always consider the ability of other centers to get up and running with it.

Gay: Neil, I go along with your suggestion of why not just use the higher-PEEP table? But I would add one more thing. I'd always thought of it as a more appropriate treatment for patients with so-called non-pulmonary ARDS patients, with whom you might get away with higher PEEP. Wouldn't you then have a better opportunity to just use that higher PEEP if you confined it to that patient population?

Talmor: I'd argue that patients with so-called non-pulmonary ARDS are the ones in whom you really want to know the chest wall component and to titrate based on that, so I would say no. The point is to individualize the therapy. It's a major misunderstanding of our paper to say that it was a high-PEEP versus low-PEEP trial. It

wasn't. It's about individualizing to the patient's physiology, based on certain assumptions; the name of the game for us is individualization.

I've been doing this for 9 years, and we can still get fooled: you're sure you'll have to increase the PEEP in a certain patient, but then you place the balloon and it shows you that you don't, or vice versa. Consider intra-abdominal hypertension in a medical patient; you see the skinniest medical patient with a soft abdomen, but they require a higher PEEP based on our method.

Fessler: Dan, the positioning of the esophageal balloon is somewhat problematic, and was even in your study. In some patients you couldn't pass it into the stomach, and so you positioned it somewhat arbitrarily. If you move the balloon several centimeters up the esophagus, how much does that change the P_{es} measurement?

Talmor: That is a misinterpretation of the paper. In some patients it was difficult to pass it below the lower esophageal junction, so we couldn't measure gastric pressure, but we could and did optimally place the balloon by looking at cardiac oscillations, which is the way to do it. In spontaneously breathing patients you'd look at an occlusion test and things like that, but you can't do that in patients who aren't making spontaneous respirations. And the balloon seems to stay put unless someone pulls it, and a few centimeters up or down does not seem to make a big difference.

Gentile: I've placed several hundred of these over the years, for various reasons, and the most useful one is a nasogastric tube with a balloon on it, which doesn't add any extra lines or tubes to the patient. You put it in during intubation, and it seems to be more helpful than having to put another tube in after the nasogastric and Dobhoff tubes are in.

Talmor: Is the nasogastric tube with the integrated esophageal balloon proprietary to one ventilator company?

Siobal: That was a BiCore product. A couple years ago, Alex Adams published an abstract[1] of a study in which he took a regular nasogastric tube, positioned it in the esophagus, and then attached a manometer to the bedside monitor, and it correlated with the esophageal balloon measurements.

What about lateral decubitus positioning? Does it improve the measurement accuracy? We also occasionally find esophageal balloon measurements useful in morbidly obese patients, where you want to show the intensive care team that we need to keep this patient on PEEP of 20 cm H_2O and do spontaneous breathing trials from high PEEP so we can wean them of the ventilator without the lungs collapsing.

1. Adams A, Shapiro R, Armaganides A. A potential for monitoring esophageal pressure with open-ended, fluid-filled, or air-filled catheters (abstract). Respir Care 2001;46(10):1108.

Talmor: We haven't used nasogastric tubes the way you described, but we have looked at the relationship between gastric pressure and esophageal pressure, and they correlate pretty nicely, so there's a possibility that we may be able to titrate PEEP based on gastric pressure. We haven't tried different body positions. Your point about obese patients is really good; when we do the measurements, we find that the chest wall compliance in obese patients is normal. Then we need to look at the absolute pressures and titrate PEEP based on those baseline pressures rather than looking at the chest wall compliance, which can often be quite good in these patients. These patients definitely benefit from this.

Branson: I've placed a lot of these too. When the nasogastric tube is positioned optimally for esophageal pressure measurement, it's not positioned optimally to empty the stomach, so you

can get into a push-and-pull with the nurses—literally, with them putting it where they need it, and me trying to put it where I need it. I know you can place it and a therapist can place it, but how often does it become displaced and how often do you have to reposition it? As somebody who works in a trauma intensive care unit, where things change quickly, I think the ARDS Network table doesn't provide the ability to deliver the necessary PEEP.

MacIntyre: Use the higher table, Rich!

Branson: Oftentimes we are looking at lung mechanics and not really worrying so much about oxygenation. Dan's ideas have a lot of interest in the group I work with.

Talmor: One thing that I hope was clear in the paper is that we usually made these measurements only once a day. We found that after optimally recruiting the lung that one time, the patients usually became stable, at least from a respiratory standpoint. If the patient's situation changed, and of course there are unstable trauma patients where that could easily happen, we would make the measurements more often. It's not something you're measuring every half hour, and you have to make sure it's in the right place before you make the measurements.

With regard to the other tubes in the esophagus, we've found no measurement artifact with either a Dobhoff tube or a regular nasogastric tube. The times we've run into trouble is when there are 2 tubes down there and the esophageal balloon gets in the middle between the 2 tubes, and because of the very low inflation volume the balloon might not be touching the sides of the esophagus and that throws your measurements off. So a surgical patient with a nasogastric tube and another tube down into the jejunum or something is a problem.

Sessler: To me, the individualization is really attractive, and I liked

that about the Mercat et al[1] study, but I think there was an over-inflation problem in the patients with milder ALI. Your individualized approach requires more work, Dan. Is Mercat's technique another way of modifying PEEP based on individual patient characteristics?

Also, was there a difference in rates of air leak? You didn't present anything on air leaks.

1. Mercat A, Richard, JC, Vielle B, Jaber S, Osman D, Diehl JL, et al; Expiratory Pressure (Express) Study Group. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA 2008;299(6):646-655.

Talmor: There were no incidents of air leak in any patients in either group.

I'm not sure I fully understand the Mercat study. By limiting the PEEP to a plateau pressure of 28 cm H_2O, you're actually giving your sickest, least compliant patients the least PEEP, which is not something I would do, and it doesn't sound like Rich would either. By increasing their PEEP in the sickest patients you're very quickly going to get to a plateau pressure of 28 cm H_2O, while the least sick patients are going to get the most PEEP. That is very different from my practice, so I can't say I really understand that study.

I'm postulating now, but I think part of their rationale was a strong belief among many French intensivists that a plateau pressure of greater than 28 cm H_2O can lead to right-ventricular failure. We're very different from the Mercat study, and I wouldn't recommend using that as an alternative. It may be better, but I wouldn't use it as an alternative; they are completely different strategies.

Hess: Dan, the question, as you suggested, is, "Well, maybe gastric pressure is as good as esophageal pressure?" If that's the case, then why not use bladder pressure? That's a whole lot easier to measure and most all these

patients already have a Foley catheter. Another comment I would make is, if we're going to individualize the PEEP to lung mechanics, I would consider the stress index. I'm intrigued by the stress index, and I've been looking at it in the intensive care unit. I haven't been doing the curve fitting and calculating the b-coefficient, but I can tell you that if you look for it, you can see the curve change as you change the PEEP and tidal volume.

Talmor: We have looked at bladder pressure and gastric pressure, and there's a similar correlation; bladder pressure may be useful as well. One of the problems with bladder pressure is that by the time the signal gets down to the bladder, you lose the respiratory variation. So you're essentially left with one number, it's kind of a flat tracing, as opposed to the gastric pressure, where you still see respiratory variation. In terms of the stress index, this is anecdotal, but we compared our measurements to the stress index and they seemed to show signal in the same direction. I think there's a formal study going on comparing our measurements to the stress index.

MacIntyre: Hank, you mentioned using esophageal pressure to predict the outcome of a spontaneous breathing trial. That's different than what we've been talking about, but I don't understand why we need all these predictors for spontaneous breathing trials. Why not just do it?

Epstein: Agreed.

Fessler: I think all three of us are on the same page.

MacIntyre: I spend a lot of time reviewing papers for Dean and other editors, and paper after paper after paper keeps trying to find ways of predicting the outcome of a spontaneous breathing trial. It befuddles me. Just do the trial.