Transpulmonary pressure: importance and limits

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Abstract: Transpulmonary pressure (P_L) is computed as the difference between airway pressure and pleural pressure and separates the pressure delivered to the lung from the one acting on chest wall and abdomen. Pleural pressure is measured as esophageal pressure (P_{ES}) through dedicated catheters provided with esophageal balloons. We discuss the role of P_L in assessing the effects of mechanical ventilation in patients with acute respiratory distress syndrome (ARDS). In the supine position, directly measured P_L represents the pressure acting on the alveoli and airways. Because there is a pressure gradient in the pleural space from the non-dependent to the dependent zones, the pressure in the esophagus probably represents the pressure at a mid-level between sternal and vertebral regions. For this reason, it has been proposed to set the end-expiratory pressure in order to get a positive value of P_L. This improves oxygenation and compliance. P_L can also be estimated from airway pressure plateau and the ratio of lung to respiratory elastance (elastance-derived method). Some data suggest that this latter calculation may better estimate P_L in the nondependent lung zones, at risk for hyperinflation. Elastance-derived P_L at end-inspiration ($P_{Lend-insp}$) may be a good surrogate of end-inspiratory lung stress for the "baby lung", at least in non-obese patients. Limiting end-inspiratory P_L to 20–25 cmH$_2$O appears physiologically sound to mitigate ventilator-induced lung injury (VILI). Last, lung driving pressure (ΔP_L) reflects the tidal distending pressure. Changes in P_L may also be assessed during assisted breathing to take into account the additive effects of spontaneous breathing and mechanical breaths on lung distension. In summary, despite limitations, assessment of P_L allows a deeper understanding of the risk of VILI and may potentially help tailor ventilator settings.

Keywords: Acute respiratory distress syndrome (ARDS); ventilator-induced lung injury (VILI); respiratory mechanics; driving pressure; mechanical ventilation; esophageal pressure (P_{ES})

Introduction

Mechanical ventilation to restore aeration in the collapsed lung and reverse hypoxemia is a life-saving treatment for patients with the acute respiratory distress syndrome (ARDS). However, despite recent advances in the diagnosis and management, ARDS mortality remain as high as 30–45%, with inappropriate ventilatory settings contributing to morbidity through the so-called ventilator-induced lung injury (VILI) (1,2). Ventilator induced lung injury is a dysregulated inflammatory response that occurs as a means of excessive volume/pressure (volu- and barotrauma) load in the aerated lung (i.e., the baby lung) along with the cyclic opening and closing of distal airways and/or flooded or collapsed alveoli during tidal ventilation (atelectrauma) (1,3,4). Since its introduction in 1950s, mechanical ventilation was aimed at treating the impairment in gas exchange; recent years have witnessed a radical shift towards

a mechanistic 'lung protective' approach, so that nowadays limiting VILI has arisen as a priority in the management of patients with ARDS (5). Limiting tidal volume (V_T) to 6 mL/kg of predicted body weight (PBW) with plateau pressure (P_{PLAT}) within 30 cmH$_2$O for most patients has been shown to improve survival as compared to higher V_T (12 mL/kg of PBW) (6). Subsequent physiological studies have also suggested that further reduction of V_T to 3–4 mL/kg may benefit patients who are at higher risk of overdistension (7-10).

Respiratory system compliance (C_{RS}) is directly affected by the size of the aerated lung. Amato *et al.* suggested that the impact of tidal ventilation on lung injury could be better predicted if V_T is normalized to C_{RS} rather than to PBW. The ratio V_T/C_{RS} is the driving pressure of the respiratory system (ΔP), and can be easily calculated at the bedside as P_{PLAT}-PEEP. It was shown to be the final mediator of the effects of lowering V_T and P_{PLAT} on mortality (11). Essentially, ΔP estimates the mechanical distortion provided by V_T to the baby lung (i.e., the dynamic strain), while P_{PLAT} roughly measures the pressure delivered to the baby lung with V_T and PEEP (the lung stress): both contribute to rate the risk of barotrauma. Introducing transpulmonary pressure (P_L) into the bedside management has then been proposed for two main purposes: know the influence of the chest wall on airway pressure and determine the pressure needed to keep the lung open. In addition, esophageal pressure (P_{ES}) is essential to assess patient's effort and the P_L generated during partial ventilatory support.

In the present review, we will describe how P_L helps assessing mechanical ventilation harms and benefits, its importance and limitations in respiratory mechanics monitoring and its possible usefulness in tailoring patient's management. Because P_L is the pressure distending the lungs, it is referred to as P_L.

P_L allows to differentiate lungs and chest wall

Airway pressure is the sum of the pressure delivered to move the lung, the chest wall and the pressure required to overcome the resistive forces (when flow is present). In the absence of flow and if airways are open, airway pressure is equilibrated with alveolar pressure. This pressure, being also needed to overcome chest wall, does not always reliably reflect the pressure load the lung is exposed to.

Consequently, P_{PLAT} during a short end-inspiratory occlusion (0.3–0.5 s) and total PEEP (and consequently ΔP) displayed by the ventilator, being measured at airway

opening, represent alveolar pressure but are only surrogates of the actual pressure acting on the lung, which is best assessed with P_L.

P_L is the pressure delivered to the lung independently from the effects of the chest wall and the abdomen and is computed as the difference between airway pressure and pleural pressure. While alveolar pressure is applied to overcome the elastic recoil of the respiratory system [(respiratory system elastance (E_{RS})], that is the sum of the elastance of the lung (E_L) and the elastance of the chest wall (E_{CW}), P_L, if measured in the absence of flow, represents the actual pressure dissipated across the lung tissue.

Given that both pleural pressure absolute values and chest wall elastance (changes in the pleural pressure due to changes in lung volume) are often impaired in a variable proportion during ARDS (12-15), this concept has relevant implications in clinical practice.

First, PEEP applied on the alveoli needs to overcome pleural pressure to generate recruitment. The effective recruiting PEEP is the one acting on the lung independently from pleural pressure (16,17).

Second, during tidal ventilation, high alveolar pressure may not be injurious *per se* if it is required to overcome E_{CW} rather than being dissipated across the alveoli: in a 'proof of concept' study, in 1988 Dreyfuss *et al.* showed that lesional pulmonary edema occurs in paralyzed healthy animals during pressure-control ventilation with high V_T and airway pressures, but not in those ventilated with similar airway pressures and lower V_T because of straps applied around their abdomens and chests. The straps were a simple way to raise E_{CW}; therefore, for the same airway pressure or P_{PLAT}, the lung distending pressure (i.e., P_L) was lower and non-injurious. Their experiments showed that volume (i.e., lung stretching), not airway pressure, was the most important factor in determining injury, a finding that led them to coin the term 'volutrauma' (18). We now interpret these findings as the indirect demonstration of the importance of P_L in determining 'lung trauma' and injury, which indeed do not occur if P_L is maintained within safe limits, no matter how high airway and alveolar pressures are.

P_{ES} vs. pleural pressure

Direct pleural pressure measurement is complex in experimental conditions and even harder in the clinical setting. Since 1950s, P_{ES} measured through dedicated balloons has been proposed to estimate pleural pressure and compute P_L (19). Esophageal manometry has drawbacks
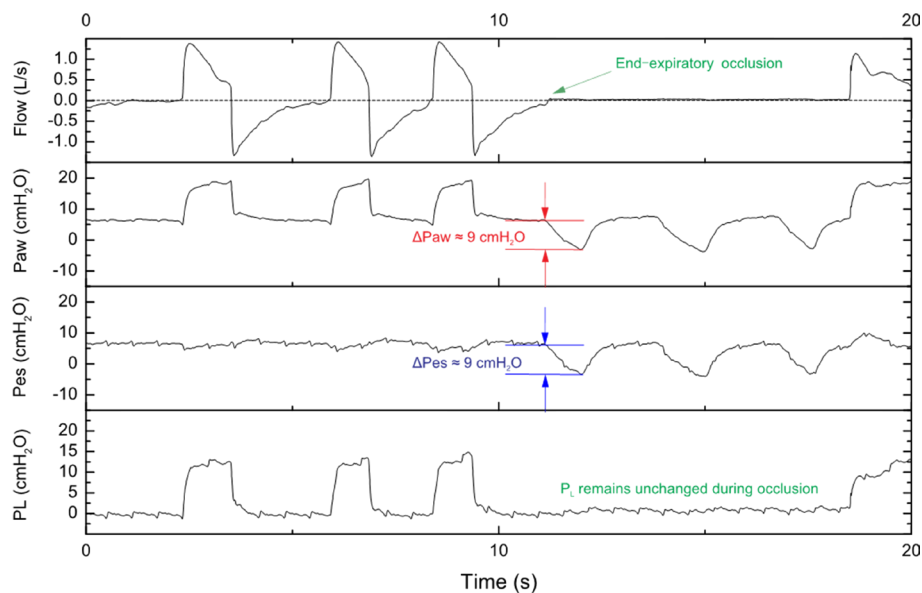
Figure 1 Negative pressure occlusion test during spontaneous breathing. During an end-expiratory occlusion, the patient generated three spontaneously inspiratory efforts (negative pleural pressure) against the occluded airway. The negative change in airway pressure (ΔPaw) is identical with the negative change in esophageal pressure (ΔPes). Also, the transpulmonary pressure remains unchanged during end-expiratory occlusion. In this case, the change in esophageal pressure can be used to surrogate the change in pleural pressure. P_L, transpulmonary pressure.

that indeed have limited its use in the clinical field until the last decade: a great effort has been made to standardize the technical issues concerning catheter placement and signal validation (20). In addition, the recent renewed interest in the topic has provided data that allow a deeper understanding of P_{ES} meaning and validity in estimating pleural pressure, computing P_L and understanding respiratory mechanics (21-24).

P_L vs. transalveolar pressure

P_L is calculated as the difference between the airway pressure and P_{ES}. When flow is absent, the role of resistive forces is ruled out and airway pressure is equilibrated with alveolar pressure, with P_L corresponding to transalveolar pressure, provided that airways are fully open (25). Essentially, during end-inspiratory and end-expiratory occlusions, the difference between airway pressure and P_{ES} is the actual pressure the alveoli are exposed to.

Technique

P_{ES} is measured through dedicated catheters endowed with esophageal balloon associated or not with gastric balloon

for contemporaneous measurement of gastric pressure.

Briefly, the esophageal catheter is transorally/transnasally inserted in the esophagus, gently advanced to the stomach (usual depth 55–60 cm) and then the balloon is inflated with the minimum non-stress volume recommended by the manufacturer. An underfilled balloon does not properly transmit P_{ES}, whereas an overfilled balloon overestimates the value of the surrounding pressure. One technique is to start with inserting the catheter down in the stomach and, after confirming the intragastric placement of the balloon with a gentle epigastric compression, the catheter is progressively withdrawn into the esophagus, as suggested by the appearance of cardiac artifacts on the signal. The validity of the measured P_{ES} can be confirmed by either a negative pressure occlusion test (26) during spontaneous breathing (*Figure 1*) or a positive pressure occlusion test during passive ventilation (*Figure 2*). In spontaneous breathing patients, during an end-expiratory occlusion, a negative change in the intrathoracic pressure by patient's inspiratory effort generates a consistent change in the airway pressure, as P_L is necessarily unmodified given the constant lung volume. In patients without spontaneous breathing the change in the intrathoracic pressure is provided by a gentle compression on the chest and is positive, with similar
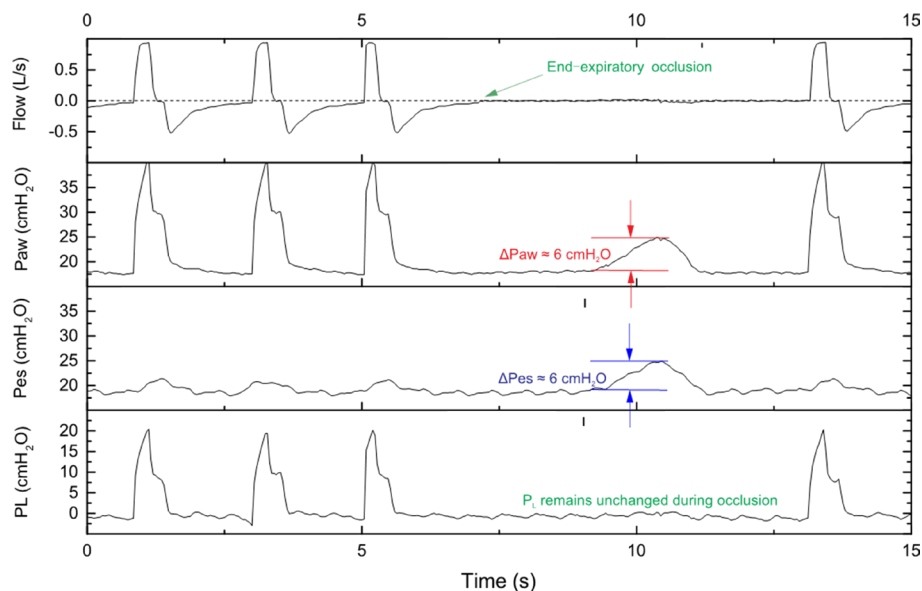
Figure 2 Positive pressure occlusion test during passive ventilation. During an end-expiratory occlusion, the patient was not able to generate any inspiratory effort since the patient was ventilated passively (no spontaneous effort for inspiration). A clinician need to manually compress the chest wall or abdomen to generate a transit increase in pleural pressure (ΔPes). The positive change in airway pressure (ΔPaw) is identical with the positive change in esophageal pressure. Also, the transpulmonary pressure remains unchanged during end-expiratory occlusion. In this case, the change in esophageal pressure can be used to surrogate the change in pleural pressure. P_L, transpulmonary pressure.

principle and mechanism of action. Ratio of the change in P_{ES} to the change in airway pressure within 0.8–1.2 is an accepted value to confirm the validity of the measure.

A more detailed technical description of the procedure along with a precise instructional video (https://www.edge-cdn.net/video_1059118?playerskin=37016) have been recently published and made available online by the PLUG working group of the European Society of Intensive Care Medicine (21).

Pleural pressure gradient

Uncertainties exist concerning the reliability of P_{ES} in estimating pleural pressure. A vertical gradient in the pleural pressure in the supine patient has been documented in several experimental conditions, with higher values documented in dorsal (dependent) and lower in ventral (non-dependent) lung regions (27,28). This raised concerns about the lung regions in which P_{ES} allows to compute the actual distending pressure. Experimental data and translational results from our group showed that in the supine position pleural pressure increases from sternal to vertebral regions because of a vertical gradient generated by superimposed pressure. This gradient appears magnified by lung injury

but is also present in the healthy lung. In such a context, P_{ES} reliably estimates pleural pressure in the area surrounding the esophagus, which is at a mid-value between ventral non-dependent and dorsal dependent lung regions (24,29).

Direct measurement of P_L at end-expiration

Description

Directly measured P_L at end expiration is computed as follows (14):

$$P_{Lend-exp} = PEEP_{TOT} - P_{ESend-exp}$$

where $PEEP_{TOT}$ and $P_{ESend-exp}$ are airway and esophageal pressure during an end-expiratory occlusion.

Some authors have proposed to subtract 5 cmH_2O from the value of P_{ES} to account for the weight of the mediastinum, but uncertainties exist regarding the validity of this approximation in ICU patients (16,30).

Application

The optimal PEEP setting protocol during ARDS is hotly debated. Low-tidal volumes tend to reduce alveolar

recruitment and further impair oxygenation: both effects can be reversed by PEEP (31,32). Moreover, PEEP-induced lung recruitment increases the size of the baby lung (i.e., the functional residual capacity) and, for a given V_T, may reduce lung dynamic strain and mitigate lung injury (33-35).

Nevertheless, it is widely accepted that PEEP setting should aim to a balance between its capability to re-open the collapsed lung and the unavoidable damage generated in the already open alveoli that occurs as a means of static stress and strain in the baby lung. Hence, over the last decade, great effort has been made to identify the PEEP-setting strategy that best optimizes lung recruitment without producing excessive alveolar overdistension; PEEP titration methods based on C_{RS} (36-38), oxygenation and shunt values (39,40) and pressure-volume curve (41) have been proposed. Three different randomized studies comparing higher versus lower levels of PEEP, in which higher PEEP values were set according to respiratory mechanics (37) or oxygenation impairment (39,40), failed to detect a significant effect on survival, although some benefits (less use of rescue therapy, reduced ventilation duration) were demonstrated in some studies. A meta-analysis showed a significant survival benefit in most severe patients treated with higher PEEP (42), but the most relevant drawback of such 'universal' approach stays in the fact that lung recruitability (increase in the size of the baby lung as a response to PEEP) may significantly vary among patients according to different degrees of lung inhomogeneity: high PEEP in patients with low recruitability may enhance lung injury in the aerated lung, while low PEEP in potentially recruiting patients cannot fully exert its beneficial effects (41,43,44).

Thus, it appears physiologically sound that PEEP setting should be rather mechanistically individualized on patient's needs and requirements. In this sense, in 2008, Talmor *et al.* reported the results of a pilot mono centre randomized trial in patients with ARDS (PaO_2/FiO_2 ≤300 mmHg) assessing the effect on oxygenation of a PEEP-setting protocol measuring P_{ES} in all patients to achieve a positive P_L, computed with the directly-measured method with no correction for the weight of the mediastinum (17). The authors showed a significant increase in oxygenation, compliance of the respiratory system and a trend to an improved clinical outcome in patients receiving higher PEEP based on P_L. Despite the interest of these results, it is not possible to discriminate whether the positive P_L or the higher absolute PEEP values irrespectively of P_{ES} drove the observed results. A larger multicentre study with similar design is currently ongoing

and will allow to refine more concrete conclusions (45).

Given that the directly-measured method allows to measure P_L in the lung surrounding the esophagus, setting PEEP according to the directly-measured P_{ES} may allow to overcome the superimposed pressure in that specific area, which likely is at the edge between dependent and non-dependent lung regions and could be worthy recruiting to minimize the risk of recurrent alveolar opening and closure. Results from clinical trials will shed some light on this important clinical question.

The safety of such approach may be also limited by the risk of hyperinflation of the baby lung, which indeed is the most relevant mechanism of lung injury (46).

In addition, some controversies have been raised around the concept of the absolute value of P_{ES} for this titration, highlighting that it did not represent the lung weight measured by CT scan nor correlates with ARDS severity; importantly, PEEP set to achieve a positive P_L according to this protocol provides settings that seem unrelated to lung recruitability (44,47).

The elastance derived method at end-inspiration

Regional overdistension is probably the key mediator of VILI and the global effect of PEEP and V_T needs to be addressed with criteria assessing tidal hyperinflation (35,46). P_L and the P_{ES} may help rate the degree of overdistension, as explained below.

Definition

The most accepted clinical method for measuring regional overdistension in the baby lung is the total inflation pressure (P_{PLAT}) due to V_T and PEEP. P_{PLAT} and the change in pressure (driving pressure, ΔP) during tidal ventilation have been proposed to better assess this risk, as they respectively surrogate the measure of lung stress and dynamic strain.

P_{PLAT} and ΔP are measured in the airways: P_L at end-inspiration ($P_{Lend-insp}$) and lung driving pressure (ΔP_L) are the parameters representing the corresponding pressure loads in the lung independently from the effects of the chest wall.

Three approaches are available for computing $P_{Lend-insp}$:

(I)   The directly-measured method already discussed, using absolute values (17):

$$P_{Lend-insp} = P_{PLAT} - P_{ESend-insp}$$

where P_{PLAT} and $P_{ESend-insp}$ are airway and esophageal pressure during an end-expiratory occlusion.

(II) The release-derived method (47):

$$P_{Lend-insp} = (P_{PLAT} - P_{ESend-insp}) + P_{ESzeep}$$

The release-derived $P_{Lend-exp}$ represents the total amount of P_L increase from ZEEP to PEEP.

(III) The elastance-derived method: this method does not require the measurement of P_{ES} atmospheric pressure but simply the change in P_{ES} (33):

$$P_{Lend-insp} = P_{PLAT} \times (E_L/E_{RS})$$

with E_L and E_{RS} respectively representing the E_L and of the respiratory system. E_L can be measured from changes in P_L. E_{CW} can also be calculated from P_{ES} and subsequently E_L calculated as $E_{RS} - E_{CW}$.

$$E_L = [(P_{PLAT} - P_{ESend-insp}) - (PEEP_{TOT} - P_{ESend-exp})]/V_T$$
$$E_{RS} = (P_{PLAT} - PEEP_{TOT})/V_T$$

Given that

$$\Delta P = (P_{PLAT} - PEEP_{TOT})$$

$P_{Lend-insp}$ according to the elastance derived method can be also expressed as

$$P_{Lend-insp} = P_{PLAT} \times (\Delta P_L/\Delta P)$$

According to the elastance- and release-derived methods, P_L and P_{ES} are interpreted to partition the change in the elastic pressure of the respiratory system between the lung and the chest wall. Both these methods rely on the assumption that P_L is 0 at atmospheric pressure, are highly correlated and consistently represent the total increase in lung stress due to PEEP and V_T (i.e., static and dynamic) from atmospheric to the inflation pressure.

Conversely, the directly measured method provides significantly lower values, potentially underestimating the risk of overdistension (47).

Assessment of $P_{Lend-insp}$ seems important to fully understand the effect of different ventilator settings and to stratify patients' severity, in order to optimize interventions and define the need for rescue therapies (48).

A debate has arisen from the evidence that the direct measurement and the release-derived methods provide values that are not interchangeable (47,49). Recent preliminary data from our group suggest that both approaches may give interesting results for clinical application but with different meanings: in particular, the directly measured $P_{Lend-insp}$ describes the actual $P_{Lend-insp}$ in the area situated at the level of the esophagus. This is a region that is often collapsed, at risk for repeated closing and opening, and less exposed to the risk of overdistension than non-dependent regions. On the contrary, in non-obese patients, the elastance derived $P_{Lend-insp}$ could surrogate the P_L mostly in the non-dependent lung regions, which are most exposed to lung injury due to hyperinflation (29).

Application

The elastance-derived $P_{Lend-insp}$ is the lung stress and is mathematically coupled to the ΔP_L, being itself a surrogate of lung strain (50,51). Large datasets describing the epidemiology of $P_{Lend-insp}$ are not available, but it could represent a novel tool to better target and determine the effects of mechanical ventilation during ARDS. It may potentially be also used during assisted ventilation to assess the risk of patient self-inflicted lung injury, since P_{PLAT} and $P_{Lend-insp}$ measurement seems feasible in such context (52,53).

Limiting elastance-derived $P_{Lend-insp}$ lower than 20-25 cmH_2O is probably a reasonable approach (21,33,48): unfortunately, setting PEEP to achieve a positive directly measured $P_{Lend-exp}$ while keeping $P_{Lend-insp}$ below 20–25 cmH_2O is not always possible (49) when V_T is set at 6 mL/kg IBW (45).

ΔP_L

Definition

ΔP_L, defined as the difference between $P_{Lend-insp}$ and $P_{Lend-exp}$, stands for the V_T-induced lung stress and reflects the distending pressure taken by the lungs when V_T delivered. This parameter provides two potential advantages: first and similar to ΔP, ΔP_L removes the stress caused by PEEP from transpulmonary P_{PLAT}, which does not necessarily contribute to lung injury and sometimes can mitigate it (35). Second, ΔP_L has removed the distending pressure taken by the chest wall from ΔP, which is barely relevant to the risk of VILI. Hence, it sounds reasonable to suspect that ΔP_L might be better associated with the risk of VILI and even clinical outcomes than ΔP.

It is computed as:

$$\Delta P = (P_{PLAT} - PEEP_{TOT})$$
$$\Delta P_L = (P_{PLAT} - P_{ESend-insp}) - (PEEP_{TOT} - P_{ESend-exp})$$

Application

A retrospective analysis on 56 patients by Baedorf Kassis et al. (54) suggested that ΔP_L, after 24 h receiving two different PEEP strategies is associated with 28-day mortality. The

ΔP demonstrated similar association with mortality in this interventional study. In an ongoing prospective, observational study for investigating epidemiology of respiratory mechanics in ARDS (NCT02623192), ΔP and ΔP_L had similar statistical power and did not differ, suggested by receiver-operating-characteristic curve analysis (55).

From a physiological view, ΔP_L represents lung stress and should be a better surrogate of lung strain comparing to ΔP. However, both the cardiac and pulmonary circulation effects of pleural pressure may also play a role in the outcome and are not represented by ΔP_L. In addition, some studies suggested that the chest wall compliance is not so widely affected in patients with ARDS; the change in pleural pressure induced by V_T is relatively similar among the majority of patients (23), so that the ΔP may be sufficient to represent the ΔP_L in many circumstances (50).

Further physiological and epidemiological studies are required to thoroughly elucidate the potential association and/or causation between transpulmonary driving pressure, VILI and clinical outcomes.

Changes in P_L may also be assessed during assisted breathing to take into account the combined effects of spontaneous breathing and of mechanical breaths on lung distension. Indeed, the pressure generated by the patient is added to the ventilator pressure. It was shown that under similar conditions of flow and volume, P_L change is similar between controlled mechanical ventilation and pressure support ventilation. Spontaneous breathing during mechanical ventilation can cause remarkably negative swings in alveolar pressure, a mechanism by which spontaneous breathing might potentially induce lung injury on top of high changes in P_L (52).

Limitations

Although P_L provides useful information concerning respiratory physiology that may potentially help clinical decision making, a large observational study dealing with patients' management in the clinical field recently showed that P_{ES} is monitored only in approximately 1% of ARDS patients (1). Even if esophageal manometry is an old technique, different aspects have hampered the widespread diffusion in the clinical setting.

Technical aspects

Recently, newer equipment facilitates the use in the clinical setting. Naso- or oro-gastric feeding tubes equipped with one or two balloons are now available to foster the clinical feasibility of esophageal manometry; similarly, some modern ventilators have been equipped with an auxiliary port connected to a pressure transducer that allows plugging an external pressure whose signal is displayed on the ventilator screen in phase with airway pressure and flow.

Signal validation

Assessment of P_{ES} requires accuracy in esophageal balloon positioning and precision in signal validation. In order to enhance the usefulness of P_{ES} measurement, techniques for *in vivo* calibration of the esophageal balloon taking into account intra-thoracic pressure and esophageal elastance have been recently reported and appear of interest (56,57). In particular, the optimal filling volume of the balloon may significantly differ from the one reported by the manufacturer (often reported for standing spontaneously breathing patients) and is dependent on the intrathoracic pressure, i.e., needing higher volumes in the supine patient. Balloon overinflation warrants complete transmission of P_{ES} swings, but is associated with significant elevation of absolute values; conversely, balloon underfilling generates incomplete transmission of P_{ES} swings (with consequent overestimation of lung elastance) and lower absolute values. To identify the optimal individual filling volume and obtain reliable measurements, an *in vivo* calibration is necessary. The full technique suggests to record static P_{ES} at end-expiration as the balloon is inflated with increasing volumes from 0 to 8 mL: afterwards, a pressure-volume curve of the balloon is generated and its intermediate linear section graphically identified. The limits of this intermediate section are the minimum and maximum filling volumes of the balloon, while the filling volume that generates the maximum change in PES during the occlusion test represents the best filling volume (57). More simply, finding the inflation volume which gives the largest tidal swing in P_{ES} usually allows to find the best filling volume (57).

Pleural pressure gradient and interpretation

P_{ES} reliably measures pleural pressure in the lung surrounding the esophagus. It may therefore underestimate pleural pressure of the dependent regions and overestimate pleural pressure of the nondependent zones (24). Accordingly, P_L computed as the absolute difference between airway pressure and P_{ES} represents the P_L at mid-chest. As already discussed, the elastance-derived method

may give an estimate of the P_L in the non-dependent baby lung, although these data are still preliminary and may not be applicable to wide categories of patients (obese, patients in the prone position) (29).

Clinical outcome

Respiratory mechanics measurements allow better stratify severity of illness and optimize ventilator settings (58). Data fostering the clinical usefulness of P_{ES} in supporting decision making during ARDS are limited to few studies, although the results appear encouraging (17,48). We recently reported that a bundle for the assessment of respiratory mechanics including esophageal manometry leads to significant adjustments in the ventilator settings in two thirds of ARDS patients, with the final effect of improving oxygenation and reducing the risk of overdistension at the same time (58).

Conclusions

In patients with ARDS, assessment of P_L is a minimally invasive technique that allows accurate respiratory monitoring and better assessment of the physiological effects of mechanical ventilation.

Ongoing research will clarify whether and to what extent P_L is more effective than airway pressure in stratifying patients' severity, assessing the risk of VILI and predicting outcome. Preliminary data regarding its use to tailor ventilator settings appear encouraging but further adequately powered studies are warranted.

Acknowledgements

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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