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Transpulmonary pressure monitoring during mechanical ventilation: a bench-to-bedside review

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Abstract

Different ventilation strategies have been suggested in the past in patients with acute respiratory distress syndrome (ARDS). Airway pressure monitoring alone is inadequate to assure optimal ventilatory support in ARDS patients. The assessment of transpulmonary pressure (P_{TP}) can help clinicians to tailor mechanical ventilation to the individual patient needs. Transpulmonary pressure monitoring, defined as airway pressure (P_{aw}) minus intrathoracic pressure (ITP), provides essential information about chest wall mechanics and its effects on the respiratory system and lung mechanics. The positioning of an esophageal catheter is required to measure the esophageal pressure (P_{eso}), which is clinically used as a surrogate for ITP or pleural pressure (P_{pl}), and calculates the transpulmonary pressure. The benefits of such a ventilation approach are avoiding excessive lung stress and individualizing the positive end-expiratory pressure (PEEP) setting. The aim is to prevent over-distention of alveoli and the cyclic recruitment/derecruitment or shear stress of lung parenchyma, mechanisms associated with ventilator-induced lung injury (VILI). Knowledge of the real lung distending pressure, *i.e.* the transpulmonary pressure, has shown to be useful in both controlled and assisted mechanical ventilation. In the latter ventilator modes, P_{eso} measurement allows one to assess a patient's respiratory effort, patient-ventilator asynchrony, intrinsic PEEP and the calculation of work of breathing. Conditions that have an impact on $P_{eso,}$ such as abdominal hypertension, will also be discussed briefly.

Key words: abdominal pressure, esophageal pressure, transpulmonary pressure, work of breathing, mechanical ventilation

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Mechanical ventilation (MV) is a life-saving supportive treatment in patients with Acute Respiratory Distress Syndrome (ARDS). The correct management of the ventilator setting is an essential aspect in the care of these patients as MV itself can also cause significant lung damage, a process known as Ventilator-Induced Lung Injury (VILI) [1, 2]. Two main mechanisms may injure the lung during MV: firstly, the excessive distention of the alveolar wall, due to dangerously high inspiratory pressures and volumes (respectively identified by lung stress and strain); secondly, the recurring intra-tidal opening and closing of lung units whose shear stress is caused by the cyclic recruitment of collapsed tissue, probably as consequence of inadequate positive end-expiratory pressure (PEEP) levels (defined atelectrauma) [3–5].

Numerous clinical studies have evaluated different ventilator strategies aiming to minimize VILI in ARDS patients. A key study, performed by the ARDS Network, showed that a lung protective ventilation strategy, using lower tidal volumes (V_t) of 6 mL kg^{-1} of ideal body weight (IBW) and limiting plateau pressure (P_{plat}) to less than 30 cmH_2O, is associated with improvement in survival [6]. This strategy reduced the risk of VILI through limiting lung stress and/or overdistension. Although the use of lung protective ventilation is currently the standard of care, P_{plat} and V_t have been shown to be an inadequate substitute in order to assess lung stress and strain, while the suggested limits may not be safe for all ARDS patients [4, 7]. Even though three subsequent randomized controlled clinical trials evaluated the effects of higher *versus* lower PEEP, no standardized protocol has

proved to improve survival in a mixed population of ARDS patients [8–10]. The PEEP level should be set to maximize the amount of recruitable lung tissue and prevent the cyclic intra-tidal recruitment/derecruitment, while avoiding overdistension of already open lung units. However, ARDS is a heterogeneous disease and patients widely differ in the amount of edema, atelectasis, loss of lung volume and lung consolidation presented [11, 12]. Although the recently issued Berlin definition is a good step forward to classify this heterogeneity, it is far from perfect, as it does not include quantification for extravascular lung water (EVLWI) and pulmonary vascular permeability index (PVPI) as suggested by others [13, 14]. Lung recruitability is an essential parameter when selecting PEEP and the large clinical trials failed to identify any benefit in survival probably because this important factor was ignored. This hypothesis is supported by the results of two meta-analysis reports showing that higher PEEP may be beneficial in sicker patients who are characterized by a greater amount of lung edema and better lung recruitability [15, 16]. This may especially be the case in patients with secondary ARDS related to an abdominal catastrophe, with capillary leak, fluid overload and intra-abdominal hypertension (IAH) [17–19]. IAH is defined as a sustained increase in intra-abdominal pressure (IAP) above 12 mm Hg. Fluid overload is not only a major cause of second and third space fluid sequestration leading to IAH but the edema of the abdominal and chest wall will result in a decrease in compliance of both the abdominal and thoracic compartment [20]. Therefore, the same PEEP level may cause overdistension in some patients or promote alveolar recruitment of collapsed tissue in others, based on the patient's individual characteristics.

The traditional management of MV based on airway pressure monitoring limits one's possibility to tailor the ventilator setting to the individual patient. Numerous pathophysiological events have a dramatic impact on respiratory mechanics in ARDS, such as: altered chest wall (fluid overload), increased IAP (capillary leak, fluid overload), amount of lung edema (increased EVLWI and PVPI) and collapse, distribution and asymmetry of lung disease (primary *versus* secondary ARDS), *etc*. Correct understanding of the overall influence of these factors on the respiratory system is fundamental in order to individualize effective and safe MV in more complex patients.

In recent years, the assessment of transpulmonary pressure (P_{TP}) is increasingly recommended to guide mechanical ventilation as it is a bedside tool that may help clinicians to improve gas exchange while avoiding lung injury in ARDS patient [21].

In this concise review, we will focus on the physiological rationale, measurement techniques and conditions that may influence esophageal pressure (P_{eso}) and the potential clinical applications of transpulmonary pressute (P_{TP}) monitoring.

TRANSPULMONARY PRESSURE

DEFINITION

Transpulmonary pressure (P_{TP}) is the real distending force of the lung parenchyma and it is calculated as the difference between the airway pressure (P_{aw}) and the pleural pressure (P_{pl}). The air moves across the respiratory system according to a pressure gradient between the alveoli and the environment.

$$P_{TP} = P_{aw} - P_{pl}$$

This pressure gradient can be negative as during spontaneous breathing, when the respiratory muscles generate negative pressure (P_{pl}) outside the lung to move air inside the respiratory system, or it can be positive provided by the ventilator at the airway opening during controlled mechanical ventilation, or a combination of the two mechanisms during assisted mechanical ventilation.

The P_{aw} is often assumed to mirror the forces applied on the lung and used to monitor MV in clinical practice. This assumption is erroneous because P_{aw} is a measure of the resistive and elastic properties of the total respiratory system, whose behavior depends on the characteristics and interaction of its two major components: the lungs and the chest wall. Consequently, the airway driving pressure acts on two structures placed in series and the change in pleural and transpulmonary pressures is the result of the ratio between their own mechanical properties (Fig. 1). Under static conditions (*i.e.*, no airflow), elastance describes the elastic properties of the respiratory system and is defined as the pressure required to inflate 1 liter above its resting position [22]. As elastance of the respiratory system is usually increased in ARDS, accordingly we can only predict lung behavior if chest wall elastance remains normal. Unfortunately, chest wall alterations are common in ARDS patients and cannot be easily predicted [4, 12, 22–24]. Obesity, increased IAP, chest wall deformities, resuscitation with large fluid volumes, pleural effusion and other conditions, all increase chest wall elastance [25–27]. A stiffer chest wall entails higher pleural pressures because greater part of the driving pressure is required to move the chest wall. The consequence is that the same P_{aw} can generate dramatically different transpulmonary pressures and pleural pressures depending on the chest wall properties.

Different models have been proposed to calculate the transpulmonary pressure during MV (Table 1). All these strategies estimate P_{TP} through the measurement of P_{aw} and esophageal pressure (P_{eso}), which is the only clinically available surrogate of P_{pl}. The rationale and limitations of P_{eso} measurement will be discussed in depth in the following section.

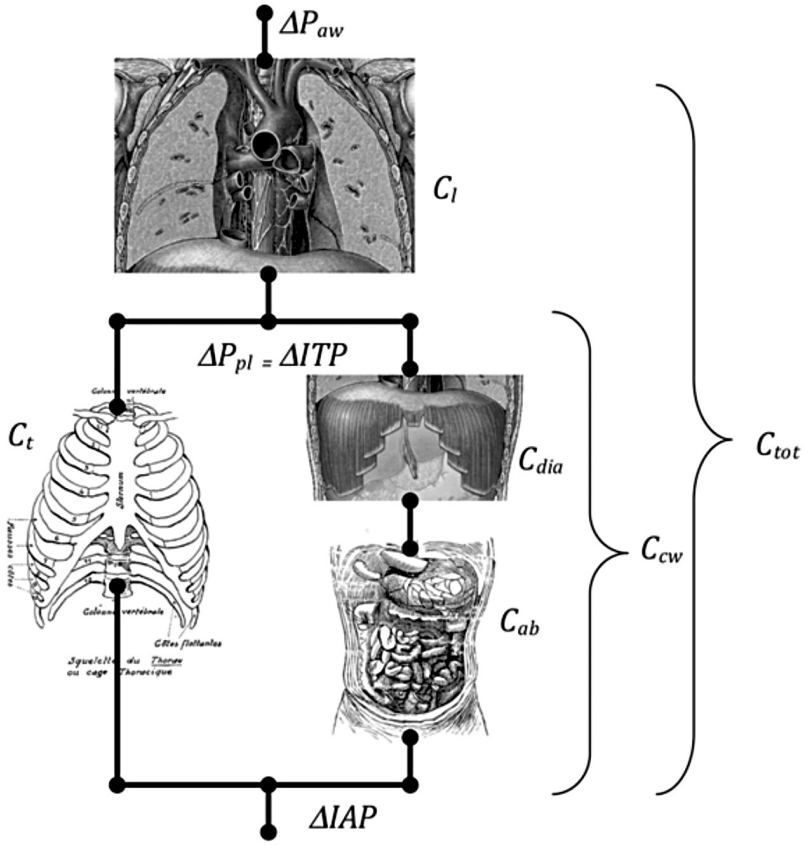

Figure 1. Interactions between different compartments. Schematic drawing with compliance separation of the different components, such as lung (C_l), diaphragm (C_{dia}) and chest wall (C_{cw}) playing a role in the transmission of pressure between thoracic (C_t) and abdominal compartments (C_{ab}) and the resultant overall compliance (C_{tot}). Based on the compliance of the different components a certain pressure change in the lungs (ΔP_{aw}) will then be transmitted via the thorax ($\Delta Ppl = \Delta ITP$) to the abdomen causing a resulting change in IAP (ΔIAP). This is called the thoracic abdominal index of transmission (TAI). Adapted from Malbrain *et al.* with permission [68]

Table 1. Methods for transpulmonary pressure computation

Transpulmonary pressure	Method	Computation
End-inspiratory P_{TP}	Elastance-derived	$P_{TP} = P_{plat} * E_L/E_{rs}$
	Release-derived	$P_{TP} = P_{plat} - (P_{esoIN} - P_{esoATM})$
End-expiratory P_{TP}	Release-derived	$P_{TP} = P_{awPEEP} - (P_{esoEX} - P_{esoATM})$
	Absolute value	$P_{TP} = P_{awPEEP} - P_{esoEX}$

P_{TP} — transpulmonary pressure; P_{plat} — plateau pressure; E_L — lung elastance; E_{rs} — respiratory system elastance; P_{esoIN} — esophageal pressure at end-inspiration; P_{esoATM} — esophageal pressure at atmospheric pressure; PEEP — positive end-expiratory pressure; P_{awPEEP} — airway pressure at PEEP; P_{esoEX} — esophageal pressure at end-expiration

ELASTANCE-DERIVED MEASUREMENT

The elastance-derived transpulmonary pressure method, originally described by Gattinoni *et al.*, calculates the end-inspiratory P_{pl} and P_{TP} through the ratio between the chest wall and lung elastance, respectively, to the respiratory system elastance [22]. In mathematical terms (with E_{rs}, respiratory system elastance, E_L lung elastance and E_{cw} chest wall elastance):

$$P_{aw} = P_{TP} + P_{pl} \text{ and } E_{rs} = E_L + E_{cw}$$

Following this, the reciprocal parts of P_{aw} spent to move outward the chest wall and to inflate the lungs can be calculated as following:

$$P_{TP} = P_{aw} \times E_L/E_{rs} \text{ and } P_{pl} = P_{aw} \times E_{cw}/E_{rs}$$

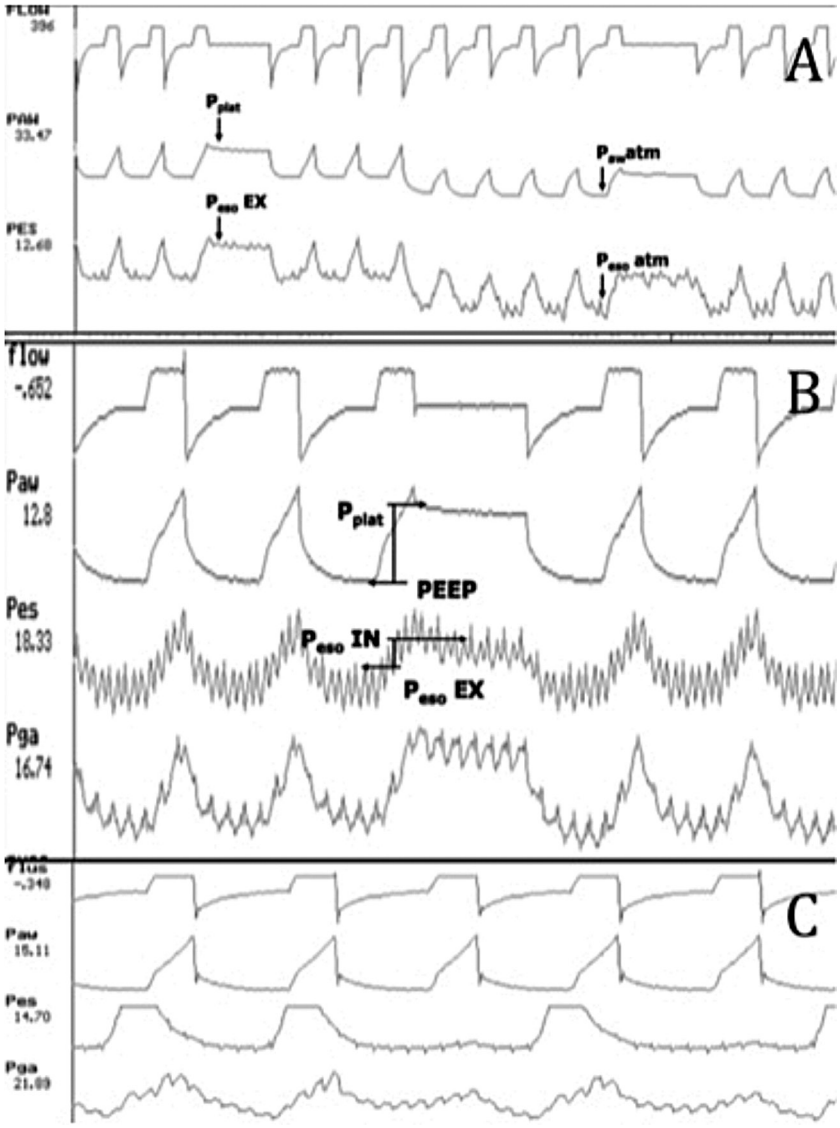

Figure 2. Tracing of flow, P_{aw}, P_{eso} and gastric pressure from patients with ARDS. **Panel A** — the arrows define the variables needed to measure the release-derived transpulmonary pressure [4, 22]. **Panel B** — the arrows show the pressure variations required to compute the lung elastance and the transpulmonary pressure using the elastance-derived transpulmonary pressure method [4]. **Panel C** — esophageal pressure tracing showing artifacts due to esophageal spasms. ARDS — Acute Respiratory Distress Syndrome; P_{plat} — plateau pressure; P_{esoIN} — esophageal pressure at end-inspiration; P_{esoATM} — esophageal pressure at atmospheric pressure; P_{esoEX} — esophageal pressure at end-expiration; PEEP — positive end expiratory pressure

This method is based on two assumptions. Firstly, as elastance is calculated using the change in P_{aw} and P_{pl} due to tidal volume, their variations must be linear during tidal volume inflation and PEEP. However, E_L depends on lung volumes and may not be linear at the extremes of the pressure-volume curve. Secondly, elastance-derived P_{TP} must be zero when P_{aw} is zero, for mathematical reasons, even if this does not means that the absolute value of P_{TP} and P_{pl} are equal to zero.

RELEASE-DERIVED MEASUREMENT

The second method described in the literature estimates end-inspiratory and end-expiratory P_{TP} as the change in P_{aw} and P_{pl} due to both tidal volume ventilation and PEEP. Transpulmonary pressure is computed as the difference between P_{aw} and P_{pl} from end-inspiratory to atmospheric pressure or from PEEP to atmospheric pressure, respectively (Fig. 2). This technique has been defined as release-derived transpulmonary pressure [4, 22].

$$P_{TP} \text{ (at end-inspiration)} = P_{aw} \text{ (at end-inspiration)} - \text{atmospheric pressure} - P_{eso} \text{ (at end-inspiration)} - P_{eso} \text{ (at atmospheric pressure)}$$

$$P_{TP} \text{ (at end-expiration)} = PEEP - P_{eso} \text{ (at PEEP)} - P_{eso} \text{ (at atmospheric pressure)}$$

DIRECT MEASUREMENT

Finally, Talmor *et al.* validated the directly-measured end-expiratory P_{TP} [28].

$$P_{TP} \text{ (at end-expiration)} = P_{aw} \text{ (at PEEP)} - P_{eso} \text{ (at PEEP)}$$

In an observational study, the authors computed end-expiratory P_{TP} as the absolute difference between PEEP and P_{eso}. Esophageal pressure averaged 17.5 ± 5.7 cm H_2O while the absolute P_{TP} was 1.5 ± 6.3 cm H_2O at end-expiration [29]. Interestingly, a significant number of patients showed a negative end-expiratory P_{TP}, which suggested the presence of lung regions at risk of intra-tidal opening/closing and collapse. The negative sign of P_{TP} is a mathematical consequence of this method and it may be due to proximal airway closure during exhalation, alveolar flooding or related to enhanced regional P_{pl} variations in edematous lungs. However, E_{cw} was not correlated with the end-expiratory P_{eso}, suggesting that the chest wall pressure-volume curve was independent from the relative point on the pressure axis [30].

The common requirement of all P_{TP} measurement techniques, as discussed above, is the need for a reliable estimate of P_{pl}, which can be clinically estimated through the measurement of P_{eso}.

ESOPHAGEAL PRESSURE

ESOPHAGEAL PRESSURE MEASUREMENT

Despite the pivotal importance of P_{pl} to evaluate lung stress and inflation during MV, it is difficult if not impossible to measure in clinical practice. The only available bedside surrogate of P_{pl} is esophageal pressure (P_{eso}). Esophageal pressure has been proposed as a substitute of P_{pl} for the first time more than 60 years ago, although its clinical role is still marginal nowadays. Two reasons limit its routine use in ARDS patients: firstly, the expertise required for catheter positioning and accurate measurement and secondly, the correct interpretation of the results for clinical implementation. A study group, named PLeUral pressure working Group (PLUG), recently came together to promote the use of P_{eso} in critically ill patients [21].

Esophageal pressure can be measured through a catheter with an air-filled balloon at the distal end; the signal is then transmitted to a pressure transducer at the proximal end for measurement (Fig. 3). A thin polyethylene tube with a standard 10-cm long balloon at the distal end essentially constitutes the catheters. The balloon covers multiple holes that transmit the changes in pressure to the transducer at the proximal end of the tube. The major advantages of this technique are that it is minimally invasive and feasible at the bedside. There are different types of esophageal catheters available on the market, each one characterized by different length, diameter, and compliance and filling volume of the balloon. These characteristics influence the measurement and must always be taken into account to ensure an accurate estimate of P_{pl}. The volume of air instilled into the balloon is typical for each catheter type. Too low instillation volumes cause P_{eso} to be underestimated, while overfilling will stretch the balloon and increase the internal balloon pressure leading to overestimation of P_{eso} [31]. Newer catheters (Fig. 3) combine the balloon with a regular nasogastric tube that can be used for enteral feeding, enabling longer monitoring of P_{eso} [32]. On the other hand, the presence of a standard nasogastric tube does not impair the measurement of P_{eso} via a balloon tipped catheter [33].

The standard positioning technique includes different phases that support correct placement. The catheter is inserted through the nostril or the mouth (accordingly to patient's need) and advanced deflated into the stomach. Now the balloon is inflated and its position inside the stomach is confirmed by the presence of positive pressure increases during inspiration, if the patient is spontaneously breathing. This intragastric pressure measurement closely reflects the IAP [34]. Subsequently the balloon is withdrawn until the P_{eso} variation becomes negative during inspiration, marking the transition into the thorax. This phase is not possible during passive MV, a circumstance in which the catheter retraction is mainly guided by the appearance of heart artifacts and a change in the absolute values of the P_{eso} curve as it passes the gastro-esophageal junction. The catheter is withdrawn a further 10 cm to fit into the lower third of the esophagus, right below the heart (the typical distance from the nostril is 35–45 cm in adults) [35].

The occlusion test, first described by Baydur *et al*., is traditionally performed to validate the correct positioning of the catheter [36]. This test consists of measuring the ratio of P_{eso} and P_{aw} change while the patient makes respiratory efforts against a closed airway. Because there is no change in volume, the transpulmonary pressure is constant and, thus, P_{eso} and P_{aw} should change equally and simultaneously. If the ratio between the change in P_{eso} and P_{aw} is between 0.8 and 1.2, then the catheter provides a reliable estimate of P_{pl}. In sedated and mechanically ventilated patients, this method was modified by applying external manual compressions on the thorax [37]. If the occlusion test is not satisfactory, first the filling volume of the catheter should be checked to rule out a potential under-filling error, and then the positioning should be repeated until correctly placed.

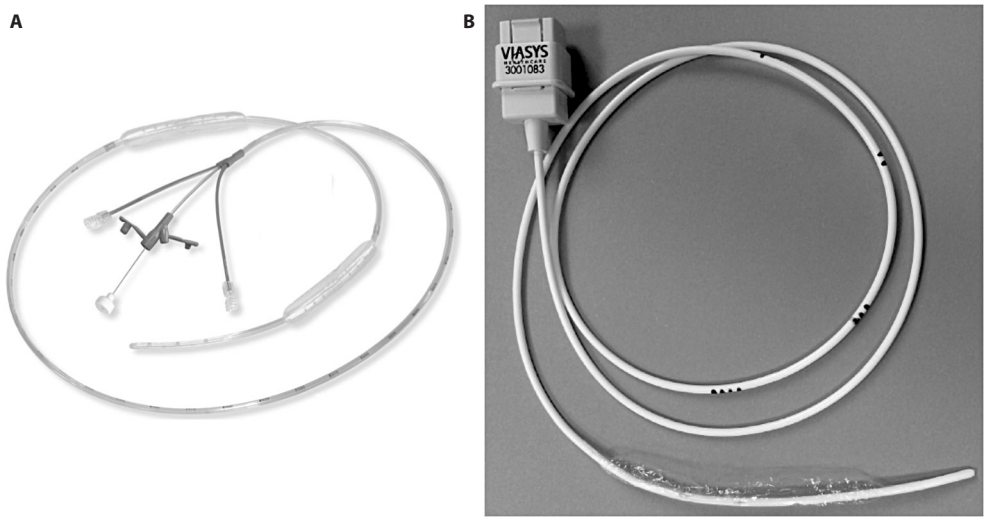

Figure 3. Examples of esophageal catheters. **Panel A** — Nutrivent (Sidam, Italy). The esophageal balloon is assembled on a regular nasogastric tube that can be used for enteral feeding. Moreover, the presence of two balloons allows simultaneous P_{eso} and intra-abdominal pressure (IAP) measurement. **Panel B** — standard esophageal balloon catheter (Smart Cath Viasys, USA)

Other techniques have been proposed in the literature, such as: fluid-filled catheters and probes with pressure sensors in the tip, or the direct recording of the pleural pressure [38, 39]. As these catheter types have not yet been clinically validated, their use is less standardized than the air-filled catheters [38]. Instead, direct recording is risky and inadvisable in clinical practice because it requires a hole through the chest wall down to the pleural space [39].

Recently, moreover, a catheter with two balloons has been clinically validated, that allows simultaneous and continuous P_{eso} and IAP pressure measurement in awake or ventilated patients [32]. This allows one to calculate the transdiaphragmatic pressure gradient which may also be related to work of breathing, especially in COPD patients with use of accessory muscles (Fig. 3).

INTERPRETING P_{ESO} MEASUREMENT

The computation of P_{TP} depends upon the assumption that P_{eso} is a good estimation of P_{pl} and so that changes in P_{eso} mirror variations in P_{pl}. This assumption is largely based upon physiological studies in healthy subjects in the upright position [40, 41].

The esophagus is anatomically adjacent to the pleural space at its lower third and P_{pl} is simply transmitted through its wall becouse it can be considered a passive membrane. However, this relationship may not hold true in the supine position when the heart, the mediastinum, and the weight of the surrounding parenchyma compress the dependent lung or when lung disease causes regional differences in parenchyma aeration and perfusion [42, 43]. Even in healthy subjects, the supine position complicates the interpretation of P_{eso} measurements. Moreover, the supine position causes a decrease in lung volumes, and a greater increase in P_{eso} compared to similar volumes in the upright position [42].

Pleural pressure in a normal subject is generally slightly negative at rest, *i.e.* at Functional Residual Capacity (FRC), as the lung tends to recoil at lower volumes than the respiratory system. In fact, the chest wall tends to move outward, preventing the lung from collapse and causing a negative P_{pl}. Moreover, P_{pl} is not evenly distributed along the pleural space but there is a gradient from the upper to the lower regions. In an upright subject, P_{pl} is higher (*i.e.*, becoming more negative) in the apical than in the basal regions. This pressure gradient is caused by the weight of the lung itself, the differences in lung and chest wall shapes, and the fact that the lung is partly supported by the rib cage and the diaphragm. This gradient is around 0.2 cm H_2O per cm of height in healthy subjects [40, 44]. This relationship holds also true in the supine position [45]. However, at very low lung volumes, irrespective of body positioning, P_{pl} may exceed atmospheric pressure (*i.e.*, becoming positive) in the dependent regions, as the elastic recoil of the lung is smaller at lower volumes and the dependent parenchyma tends to be compressed [46]. This event is even more relevant in ARDS patients, in which the wet and edematous lungs are heavier and the gravitational gradient in pleural pressure is steeper [45, 47]. This vertical gradient of P_{pl} is clinically significant as it determines a gradient of P_{TP} and, therefore, also of the lung ventilation. Because P_{eso} is measured at the lower third of the esophagus, it underestimates P_{pl} surrounding the dependent lung and overestimates the pleural pressure around the non-dependent regions. Moreover, in ARDS patients, the lung is inhomogeneous and inter-regional differences in density or elastance may not be detected by

Table 2. Studies evaluating the clinical use of transpulmonary pressure monitoring to guide mechanical ventilation in ARDS patients

Authors/year	Study design	Population	Intervention	Conclusions
Talmor *et al.* 2008 [28]	RCT	61 ARDS patients	PEEP is increased to target an end-expiratory P_{TP} of 0-10 cm H_2O	P_{TP} strategy improved oxygenation and respiratory system compliance
Grasso *et al.* 2012 [55]	Observational prospective	14 ARDS patients with refractory hypoxemia	PEEP is increased to titrate an end-inspiratory P_{TP} of 25 cm H_2O	P_{TP} strategy improved oxygenation and prevented ECMO institution

RCT — randomized controlled trial; ARDS — Acute Respiratory Distress Syndrome; PEEP — positive end-expiratory pressure; P_{TP} — transpulmonary pressure; ECMO — extra-corporeal membrane oxygenation

P_{eso} measurements. In an experimental study, Pelosi *et al.* found that P_{eso} more closely reproduced mid-lung pleural pressure in supine dogs. Despite the significant differences in the absolute values of P_{eso} and P_{pl}, changes in P_{eso} and P_{pl} were similar in response to increasing P_{aw}, thus suggesting that the variation of P_{eso} is a reasonable estimate of the variations of P_{pl} and that P_{eso} and P_{pl} were correlated at mid-lung height [45].

The calculation of absolute end-expiratory P_{TP} has raised concerns about its reliability, as numerous factors influence the absolute value of P_{eso}, such as: respiratory mechanics, lung volumes, distribution of the disease, IAP, fluid status, previous surgery, positioning, hearth and mediastinum weight and the properties of the balloon. Washko *et al.* studied the magnitude and variability of postural effects on P_{eso} in 10 healthy subjects [48]. Average P_{TP} was 7.0 cmH_2O lower in the supine than in the upright positioning at FRC. The authors found that approximately 4.1 cm H_2O, corresponding to the 58% of this difference, could be attributed to the decrease in lung volume associated with supine position. The remaining 2.9 cm H_2O change was due to horizontal displacement of the pressure-volume curve. Moreover, P_{TP} at FRC in the supine position was negative in 7 out of 10 subjects, on average -3.3 ± 3.2 cm H_2O, and it was still negative after correcting the value for the weight of the mediastinum. A study in obese patients found similar results: P_{eso} increased from 0.1 ± 2.3 cm H_2O to 9.4 ± 3.9 cm H_2O when changing from the upright to the supine position respectively [49]. This study showed how the influence of mediastinum and tissue on P_{eso} was similar in obese and normal subjects. Increased IAP and reduced chest wall compliance seemed to cause the higher P_{eso} values, both in the upright and supine positions [49, 50]. The small artifacts in P_{eso} are advocated to be predictable and acceptable compared to P_{TP} values in patients with ARDS; consequently, P_{eso} may accurately reflect P_{pl} in critically ill patients, as well as in healthy subjects [51]. In conclusion, despite some authors having promoted the use of absolute P_{eso} values, further data on critically ill patients are necessary. Especially in relation to IAP and the correlation between intragastric pressures and P_{eso}; in view of an average index of transmission between the abdominal and thoracic compartments of 50%, IAP or intragastric pressure may be a useful and more easily available surrogate parameter for P_{eso} at the bedside. Talmor, and others, found a very good correlation between IAP and P_{eso} [29, 52].

TRANSPULMONARY PRESSURE TO GUIDE MECHANICAL VENTILATION IN ARDS

In sedated and paralyzed patients, MV is currently set according to P_{aw} and tidal volume, following the ARDS Network protocol [6]. This protocol recommends to limit V_t < 6 mL kg^{-1} (IBW) and P_{plat} < 30 cm H_20 in order to improve survival. The P_{plat} pressure threshold is derived from the evidence that during spontaneous breathing total lung capacity is around a P_{TP} of 25 cm H_2O. If the patient has normal chest wall elastance, it corresponds to a P_{plat} of 30 cm H_2O and an animal study showed that this resulted in little lung inflammation and thus the absence of VILI [2].

During recent decades, the role of PEEP has changed from improving gas oxygenation towards the prevention of VILI. The main goals of PEEP are to keep the lung recruited and open, as well as to avoid the cyclic intra-tidal opening/closing of alveolar units — thus, shear stress. Because P_{plat} and V_t have been shown to be poor surrogates of stress and strain, P_{TP} has been advocated as a better guide for safe mechanical ventilation [4, 21]. In fact, as already shown, P_{aw} can be used as a surrogate for P_{TP} only if P_{pl} changed within a small range, which is not the case in clinical practice [22]. Esophageal pressure measurement allows one to titrate lung protective ventilation, tailored to the patients' needs, providing appropriate and safe P_{TP} while avoiding derecruitment and atelectrauma. Despite this strong pathophysiological rationale, clinical studies evaluating the efficacy of P_{TP}-guided mechanical ventilation are still lacking (Table 2).

In a landmark study, Talmor *et al.* showed that PEEP setting according to the end-expiratory P_{TP} was useful in ARDS patients [28]. Sixty-one patients were randomized to the standard ARDS Network protocol or to an interventional group in which PEEP was increased until achieving a P_{TP} between 0 and 10 cm H_2O at end-expiration. All patients were ventilated with a V_t of 6 mL kg^{-1}_{IBW} or lower if required to keep the end-inspiratory P_{TP} < 25 cm H_2O. End-expiratory transpulmonary pressure was computed as P_{aw} (*i.e.*, PEEP) minus the absolute P_{eso} value at end expiration, corrected for positioning artifacts: $P_{TP} = P_{aw} - (P_{eso}$

Table 3. Oxygenation – PEEP table of the control group of the EPIVent 2 trial (ClinicalTrials.gov # NCT01681225) [53]

Step	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
FiO_2	0.3	0.3	0.3	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.6	0.7	0.8	0.8	0.9	1.0	1.0
PEEP	5	8	10	10	12	14	16	18	18	20	20	20	20	22	22	22	24

FiO_2 — inspiratory oxygen fraction; PEEP — positive end-expiratory pressure

— 5 cm H_2O). Positive end-expiratory pressure was then increased until P_{TP} was greater than zero, suggesting that no expiratory lung collapse was present. The P_{eso}-guided group showed better oxygenation, with a ratio of partial oxygen tension to the inspiratory oxygen fraction (PaO_2/FiO_2) being 88 mm Hg higher than in the control group ($P = 0.002$), and better respiratory system compliance ($P = 0.001$). These effects were persistent over the entire follow-up time, at 24, 48, and 72 hours. The interventional group showed higher PEEP levels, without any hemodynamic complications, and the end-inspiratory P_{TP} never exceeded the "safe" limit of 25 cm H_2O. Although clinical outcomes and mortality were similar in the two groups, the study was not powered for these endpoints. To further explore the benefits of P_{TP} monitoring to guide PEEP setting, the same group designed a subsequent multicenter trial (EPIVent 2 – ClinicalTrials.gov # NCT01681225) [53]. Moderate and severe ARDS patients are randomized to the interventional group in which PEEP in set to maintain an end-expiratory P_{TP} greater than 0 cm H_2O, or to the control group in which PEEP is set accordingly to the ARDS Network PEEP/FiO_2 table (Table 3). The duration of the follow up in this study was prolonged from 3 to 28 days, while the primary endpoint is a composite outcome of mortality and ventilator-free days.

However, Chiumello *et al.* [54] found that setting PEEP accordingly to the absolute P_{eso} value did not correlate with patient's lung recruitability or lung weight obtained via a thoracic computed tomography (CT scan) [54]. Moreover, the chosen PEEP level also did not correlate with the severity of the disease.

A different method, targeting an open-lung approach by monitoring the end-inspiratory transpulmonary pressure, was suggested in patients with refractory hypoxemia [55]. The authors used the elastance-derived strategy to compute the actual contribution of E_{cw} on the respiratory system and set a P_{TP} of 25 cm H_2O with the purpose to optimize gas exchange and avoid extra-corporeal membrane oxygenation (ECMO). End-inspiratory P_{TP} was calculated as $P_{plat} - (P_{plat} \times E_{cw}/R_{rs})$. If the value of end-inspiratory P_{TP} was lower than the target, PEEP was increased until the upper physiological limit of 25 cm H_2O. Fourteen patients were enrolled: 7 subjects had a P_{TP} of 27.2 ± 1.2 cm H_2O and underwent ECMO, while in the other 7 patients P_{TP} averaged 16.6 ± 2.9 cm H_2O. Increasing PEEP (from 17.9 ± 1.2 to 22.3 ± 1.4 cm H_2O, $P = 0.0001$) to reach a P_{TP} of 25.3 ± 1.7 cm H_2O improved oxygenation and allowed patients to be treated with conventional ventilation.

In conclusion, both end-expiratory and end-inspiratory P_{TP} are important in ARDS and must be set accordingly to the individual patient's respiratory characteristics. Two recent studies compared the P_{TP} computation methods proposed in the literature [56, 57]. Gulati *et al.* compared the absolute value of P_{eso} *versus* the elastance-derived P_{TP} to target an end-inspiratory P_{TP} of 26 cm H_2O. The P_{pl} values with the two approaches were discordant and could differ from each other by more than 10 cm H_2O. Moreover, there was no significant correlation between the optimal PEEP levels recommended by the two methods, while the change in pressure even moved into the opposite direction in 33% of the patients [56]. Chiumello *et al.* showed similar results in 44 ARDS patients. End-expiratory P_{TP} based on the absolute P_{eso} value and on the release-derived method was: −8.0 ± 3.8 and 3.9 ± 0.9 cm H_2O at 5 cm H_2O of PEEP and −1.2 ± 3.2 and 10.6 ± 2.2 cm H_2O at 15 cm H_2O of PEEP, respectively, and did not correlate well. Absolute P_{eso} value was not related to lung weight, lung recruitability,the amount of un-aerated lung tissue on the CT scan nor to hypoxemia and chest wall elastance. Instead, there was a good correlation between the end-inspiratory P_{TP} calculated with the elastance-derived and the release-derived methods. The mean elastance- and release-derived P_{TP} was 14.4 ± 3.7 and 14.4 ± 3.8 cm H_2O at 5 cmH_2O of PEEP and 21.8 ± 5.1 and 21.8 ± 4.9 cm H_2O at 15 cmH_2O of PEEP, respectively. The results of these studies may not be surprising when taking into account the different goals of the different methods. A pathophysiological rationale must always be kept in mind when choosing one approach instead of another. Targeting an inaccurate P_{pl} could be potentially dangerous as it may lead to over- or underinflation of the lung and thus could cause VILI. On the contrary, a small observational study found a good correlation between PEEP values selected through a decremental PEEP trial with the PEEP set to achieve a P_{TP} greater than zero [58].

Finally, a recent paper has described the presence of reverse triggering in deeply sedated patients during controlled mechanical ventilation [59]. This phenomenon is caused by the diaphragmatic muscle contractions triggered by ventilator insufflations. Reverse triggering occurred during 12% to 100% of the total recording period during fully controlled mechanical ventilation. Consequently, in this

situation P_{plat} may no longer reflect $P_{TP,}$ while MV can unexpectedly increase the risk of VILI.

TRANSPULMONARY PRESSURE DURING ASSISTED MECHANICAL VENTILATION

Assisted mechanical ventilation refers to those types of ventilator support in which the patient does part of the total work of breathing (WOB). This means that, according to the equation of motion of the respiratory system, the pressure required to inflate the lungs is the sum of the pressure applied by the ventilator to the airway (P_{aw}) and the pressure generated by the respiratory muscles (P_{mus}). During triggered ventilation the active contraction of the respiratory muscles initiates the assisted breath and the generated pressure depends upon the respiratory drive and the strength of the respiratory muscles. The consequence is that P_{plat} does not mirror P_{TP} because the downward diaphragm movement causes a negative pleural pressure swing that must be added to the pressures provided by the ventilator. High spontaneous breathing efforts generate high negative pleural pressures, which can significantly increase the transpulmonary pressure despite a normal-appearing P_{plat} [60]. This phenomenon can be dangerous because P_{TP} is uncontrolled and the risk of VILI is present even if P_{plat} is below the 30 cm H_2O limit.

The rationale for assisted mechanical ventilation is to decrease the patient's respiratory effort while preventing the risk of muscular atrophy associated with controlled mechanical ventilation, the so-called ventilator-induced diaphragmatic dysfunction, because part of the WOB is still sustained by the respiratory muscles. Other benefits related to assisted respiratory support are as follows: the decrease in sedation requirements, improved patient-ventilator interaction, and the recruitment of basal diaphragmatic lung regions with a consequent gas exchange improvement.

During assisted mechanical ventilation, although a good interaction between the patient and the ventilator is essential to effectively reduce WOB, it is often difficult to assess relying only on the standard monitoring of P_{aw} and tidal volume. Esophageal pressure measurement can assess the patient's real respiratory effort, patient-ventilator asynchrony, intrinsic end-expiratory positive pressure (iPEEP) and can help with the calculation of WOB. Moreover, P_{eso} could also help one to guide the clinical titration of the support level during assisted ventilation.

The computation of WOB generated by the respiratory muscles can help the clinician to accurately weigh the amount of effort performed by the patient during assisted mechanical ventilation. Work of breathing is defined as the integral of the pressure required producing a change in volume. It is usually described on the Campbell diagram, which graphically represents the relation between the changes of P_{eso} and the volume of the respiratory system during a breath. Esophageal pressure, as a surrogate of P_{pl}, represents the effort generated by the respiratory muscles to move the chest wall, *i.e.* the patient's contribution during assisted breathing. Consequently, the Campbell diagram and the measurement of P_{eso} allow for the partitioning of WOB into its elastic, resistive, inspiratory, expiratory, lung, and chest wall (and abdominal) components. Comparing the difference between P_{eso} during an active breath and the pressure-volume curve of the relaxed chest wall can separate the resistive and elastic work. Work of breathing calculation showed that significant respiratory effort often occurs during mechanical ventilation [61]. Such measurement is important to titrate the level of ventilator support, to assess the presence of asynchrony or evaluate the performance during a weaning trial. Indeed, work of breathing proved to be a useful marker to predict weaning failure. Monitoring the trend in P_{eso} swings during a spontaneous breathing trial helped to discriminate between patients who failed versus those who succeeded in a trial [62]. The P_{eso} trend was also more accurate in predicting weaning failure than the shallow breathing index (defined as respiratory rate divided by tidal volume).

In presence of intrinsic PEEP (iPEEP), the measurement of WOB can underestimate the real oxygen consumption of the respiratory muscles because of the effort necessary to overcome iPEEP and initiate the tidal volume. If iPEEP is shown on the P_{eso} curve as a drop in P_{pl} before air flow starts, then the pressure-time product (PTP) is a more reliable measurement of oxygen consumption. The PTP is the product of the time spent in muscle contraction during inspiration as a percent of the total respiratory cycle time and the pressure generated by the muscle during inspiratory contraction [35]. The PTP was shown to discriminate between patients who fail or pass a spontaneous breathing trial [63].

Asynchrony is a major problem during assisted mechanical ventilation and is frequently clinically underestimated, which is associated with increased length of ventilation, ICU and hospital stay and mortality [64, 65]. Asynchrony derives from the mismatch between patient's respiratory drive and one or more ventilator variables controlling the breathing pattern: trigger, flow or cycle. Although very common, asynchrony may be difficult to detect and interpret without an esophageal catheter or electromyography of the diaphragm to characterize the activity of the respiratory muscles [66, 67].

CONCLUSIONS

Transpulmonary pressure is an essential measurement in order to tailor mechanical ventilation to the individual patient's needs. The benefits of P_{TP} monitoring are relevant for both controlled and assisted mechanical ventilation. In ARDS patients it can help to optimize PEEP and driving

pressure, while avoiding further lung injury (VILI). During assisted mechanical ventilation, although the precise quantitative assessment of respiratory muscle activity needs calculation, the inspiratory effort can be straightforwardly observed through the esophageal pressure swings, a clinical evaluation easy to perform at the bedside. However more clinical studies are needed to establish the definite role of P_{eso}, IAP and P_{TP} at the bedside.

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