



Assessment of different computing methods of inspiratory transpulmonary pressure in patients with multiple mechanical problems

Kamil İnci¹ · Nazlıhan Boyacı¹ · İskender Kara² · Gül Gürsel³

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Abstract

While plateau airway pressure alone is an unreliable estimate of lung overdistension inspiratory transpulmonary pressure (PL) is an important parameter to reflect it in patients with ARDS and there is no consensus about which computation method should be used to calculate it. Recent studies suggest that different formulas may lead to different tidal volume and PEEP settings. The aim of this study is to compare 3 different inspiratory PL measurement method; direct measurement (PL_D), elastance derived (PL_E) and release derived (PL_R) methods in patients with multiple mechanical abnormalities. 34 patients were included in this prospective observational study. Measurements were obtained during volume controlled mechanical ventilation in sedated and paralyzed patients. During the study day airway and esophageal pressures, flow, tidal volume were measured and elastance, inspiratory PL_E, PL_D and PL_R were calculated. Mean age of the patients was 67 ± 15 years and APACHE II score was 27 ± 7 . Most frequent diagnosis of the patients were pneumonia (71%), COPD exacerbation(56%), pleural effusion (55%) and heart failure(50%). Mean plateau pressure of the patients was 22 ± 5 cmH₂O and mean respiratory system elastance was 36.7 ± 13 cmH₂O/L. $E_L/E_{RS}\%$ was $0.75 \pm 0.35\%$. Mean expiratory transpulmonary pressure was 0.54 ± 7.7 cmH₂O (min: - 21, max: 12). Mean PL_E (18 ± 9 H₂O) was significantly higher than PL_D (13 ± 9 cmH₂O) and PL_R methods (11 ± 9 cmH₂O). There was a good agreement and there was no bias between the measurements in Bland–Altman analysis. The estimated bias was similar between the PL_D and PL_E ($- 3.12 \pm 11$ cmH₂O) and PL_E and PL_R (3.9 ± 10.9 cmH₂O) measurements. Our results suggest that standardization of calculation method of inspiratory PL is necessary before using it routinely to estimate alveolar overdistension.

Keywords Transpulmonary pressure · Mechanical ventilation · Respiratory failure · Esophageal pressure · ARDS · Intensive care

1 Introduction

Mechanical ventilation (MV) is a life saving treatment modality in patients with respiratory failure. But unless perform appropriate settings according to patient requirements and thoraco-pulmonary mechanics it might cause ventilator induced lung injury (VILI) [1]. Current standard of care for ARDS includes limiting tidal volume (V_T) and plateau pressures (P_{plat}). However, P_{plat} alone is an unreliable estimate of lung overdistension during MV especially in patients with increased chest wall elastance like chest wall edema, kyphoscoliosis, and intra-abdominal hypertension. In these situations pleural pressure increases and more force is necessary to distend the chest wall [2]. Because of this reason estimation of transpulmonary pressure (PL) is recommended [3]. Recent clinical studies suggest that adjusting ventilator

✉ İskender Kara
driskenderkara@gmail.com

¹ Critical Care Training Programme, Division of Critical Care, Department of Internal Medicine, School of Medicine, Gazi University, Ankara, Turkey

² Critical Care Training Programme, Division of Critical Care, Department of Anaesthesiology, School of Medicine, Gazi University, Ankara, Turkey

³ Critical Care Training Programme, Department of Pulmonary Critical Care Medicine, School of Medicine, Gazi University, Ankara, Turkey

settings based on PL measurements may improve oxygenation, and reduce VILI [3, 4]. The measurement of PL needs the estimation of pleural pressure (P_{pl}) from P_{es} [5–9]. PL is the real distending force of the lung parenchyma and in general it is calculated as the difference between the P_{plat} and the P_{pl} [5–11]. On the other hand there are different usage trends of PL in the treatment of ARDS patients. First, these measurements can be used to adjust PEEP. Increased chest wall elastance (E_{CW}) elevates P_{pl} and may cause negative PL. As negative PL may lead to lung or airway collapse, adjusting PEEP to achieve positive end-expiratory PL prevents collapse and optimizes lung mechanics [3, 4, 11, 12]. In general for this aim expiratory PL is used. Second, PL measurements may be used monitor for lung overdistension and to account for the increased E_{CW} during tidal breathing. For this aim measurement of inspiratory PL is recommended [3, 7]. On the other hand there are 3 different calculation method to find PL inspiratory and there is no consensus about which one should be used. Among the three approaches directly-measured method (PL_D), is the most frequently used method in literature. With this method PL is simply calculated as the absolute difference between airway and P_{es} and inspiratory P_{es} is used for this aim [3]. Another frequently used method is the elastance-derived method (PL_E) [2]. It estimates the end-inspiratory PL as the product of P_{plat} times the ratio between lung (E_L) and respiratory

system elastance (E_{RS}). In this method delta P_{es} is used as P_{es} value. Third method is release-derived method (PL_R) and is calculated as the difference between P_{aw} and P_{es} from end-inspiration to atmospheric pressure and requires disconnection from the ventilator of the patient [13, 14] (Fig. 1).

Targeting an inaccurate PL could be potentially dangerous as it may lead to over- or underinflation of the lung and there is no adequate information about the yield of PL in general ICU patients with multiple mechanical abnormalities and which measurement method should be used [15]. In general studies related with transpulmonary pressure are performed in patients with ARDS or experimental ARDS models aiming to protect patients from VILI. On the other hand, ARDS patients consists of 7–10% of ICU patients and majority of medical ICU patients are patients with chronic cardiopulmonary diseases [16–18]. They may have atelectasis, edema, risk of overdistension also during mechanical ventilation. There are very few studies investigating other patients with respiratory failure and other etiologies than ARDS. The aim of this study is to compare 3 inspiratory PL measurement methods computed in patients with multiple mechanical abnormalities.

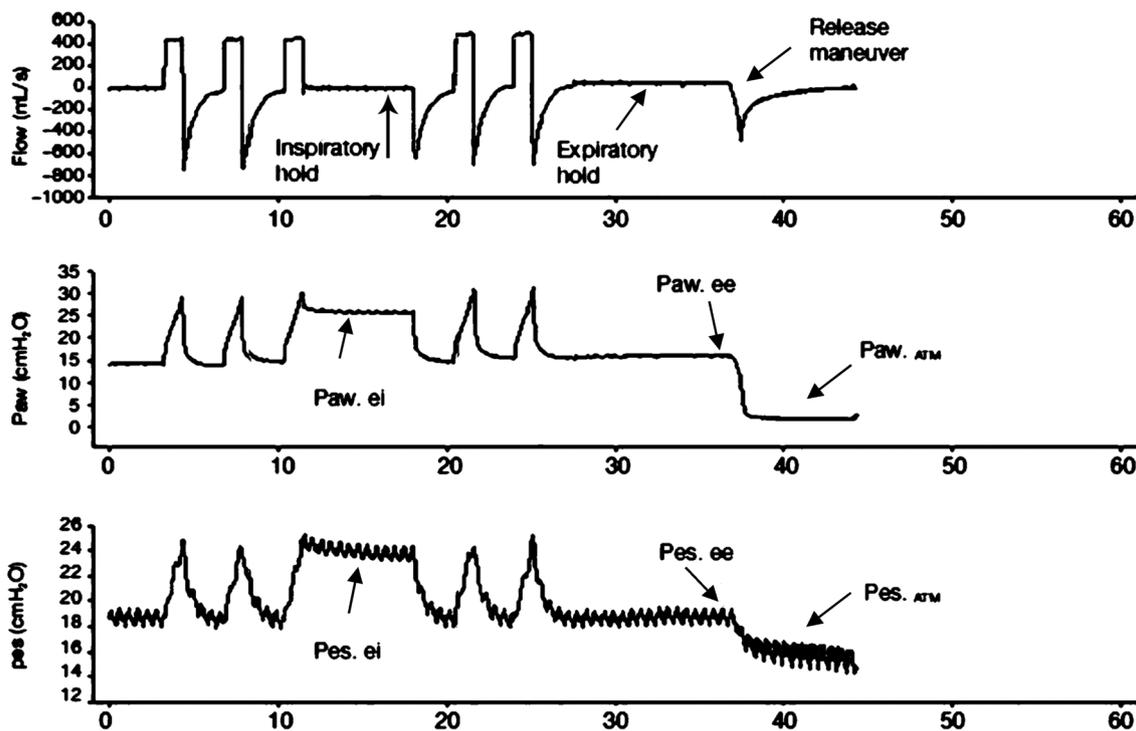


Fig. 1 Representative tracings of airway and P_{es} used to calculate transpulmonary pressure with the different methods during controlled mechanical ventilation

2 Materials and methods

2.1 Study population

The study was approved by the ethics committee of the Gazi University Faculty of Medicine (28.12.2015/166) and performed at ICU of Department of Pulmonary Critical Care Medicine of Gazi University School of Medicine. Before enrollement written informed consent was obtained by the patient or their family. The study population comprised 34 patients > 18 years old, with different pathologies. If the patient has a contraindication to esophageal catheterization (recent upper GI surgery, bleeding varices) then was excluded from the study.

2.2 Study design

All patients were intubated with an endotracheal tube no:8, sedated, paralyzed and kept in supine position. On the study day before the measurements propofol (10 mg/mL at a rate of 25–90 mg/h depending on need) was delivered intravenously and neuromuscular blocker was given till measurements were completed. The patients were ventilated with an AVEA ventilator (Viasys Health Care, Yorba Linda, CA). Baseline ventilator settings were; tidal volume 6 mL/kg, PEEP 5 cmH₂O, and respiratory rate 16 breaths/min. Respiratory rate was adjusted to maintain arterial carbon dioxide (PaCO₂) between 35 and 45 cm H₂O and FiO₂ was set to maintain arterial oxygen saturation (%SO₂) between 90 and 95%.

Eosophageal pressure (Pes) was measured with the AVEA ventilator and eosophageal balloon catheter (AVEA Smart-Cath Esophageal Pressure Monitoring Tube Set; 8 Fr adult. Viasys Health Care (Avea™; Carefusion)). First eosophageal ballon was positioned in the stomach to check the presence of positive deflection. Then, it was retracted until it reached the lower third of the esophagus(35–40 cm); in this position, an inspiratory occlusion was made to check for concordant changes in airway and esophageal pressure and inflated with 1.0–1.5 mL of air [8, 9, 19].

2.3 Measurement of respiratory mechanics

During an inspiratory and expiratory pauses, the airway and eosophageal pressures were measured. Following instrumentation, lung mechanics, peak (P_{peak}), and end-inspiratory plateau (P_{platei}) pressures; end-inspiratory esophageal pressure (P_{esei}) at P_{platei} (P_{esPlat}) at PEEP (P_{esPEEP}) and at atmospheric pressure (P_{esZEEP}) the difference between these two pressures (dPes); inspiratory PL pressures (cmH₂O); arterial blood gas values (pH, PO₂, PCO₂) were recorded. Elastance of the respiratory system (E_{RS}), lung (E_L) and chest wall (E_{CW}) during

tidal inflation was calculated from the change in P_{plat} minus PEEP divided by the tidal volume E_{RS} :

$$P_{plat} - PEEP/V_T$$

2.4 Definitions and calculations of the formulas

The following formulas were used for assessment of transpulmonary pressures and compared with each other. PL_D is based on measured ‘absolute’ value of P_{es} . This method has an assumption that absolute P_{es} by itself can be used as a surrogate of P_{pl} and then PL is directly calculated as follows using absolute values; Directly measured (PL_D) = $P_{plat-Pes,ei}$ where $P_{plat, Pes,ei}$ are airway and esophageal pressure during an end-inspiratory occlusion [3, 20].

Elastance-derived method (PL_E) does not require the measurement of P_{es} atmospheric pressure but simply the change in P_{es} : estimates the end-inspiratory PL as the product of plateau pressure times the ratio between lung (E_L) and respiratory system elastance (E_{RS}).

$$PL_E = P_{plat,ei} \times E_L/E_{RS}$$

[2, 4]

In release derived method (PL_R) transpulmonary pressure is computed as the difference between P_{plat} and P_{es} from end-inspiratory to atmospheric pressure (Fig. 1).

$$PL_R = P_{plat,ei} - (P_{es,ei} - P_{es,ATM});$$

[13, 14]

Lastly we calculated accuracy values of PL_E and PL_R accepting PL_D method as gold standard method. We accepted threshold values for PL_E as 25 cm H₂O and for the others as 20 cmH₂O for this analysis.

2.5 Statistical analysis

Data are reported as mean ± SD or as median(IQ), unless otherwise specified, as appropriate. Statistical significance was defined as $p < 0.05$. Baseline and physiologic variables were compared by Student’s *t* test for variables that were normally distributed and by Wilcoxon sign rank test for variables that were not normally distributed. To calculate correlations between the methods we used Pearson correlation coefficient. Two different formula were compared with Bland–Altman analysis (Linear regression and one sample *t* tests done for the Bland–Altman analyses). Accuracy of the different measurement methods were also calculated. SPSS version 20.0 (IBM, Armonk, NY, USA) was used for all statistical analyses and figures.

Table 1 Baseline characteristics of the study population

Age, years	67 ± 15
APACHE II	27 ± 7
Diagnosis of the patients	
Pneumonia	24 (71%)
COPD exacerbation	19 (56%)
Heart failure	17 (50%)
Acute renal failure	13 (41%)
Acute respiratory distress syndrome	10 (29%)
Pulmonary embolism	6 (18%)
Pulmonary fibrosis	9 (24%)
Atelectasis	8 (24%)
Obesity hypoventilation syndrome	8 (24%)
Pleural effusion	18 (55%)
Chest Wall disease	7 (23%)
Neurologic	6 (18%)
Comorbidities	
COPD	20 (59%)
Cardiac	27 (79%)
Malignancy	10 (29%)
Renal	7 (21%)
Others	10 (32%)

3 Results

Forty-one patients were included in the study at the beginning but in 7 patients quality of measurements were not good and they were excluded from the study (In 2 patients we noticed later that esophageal balloon was in the trachea. In 2 patients swinging of the esophageal pressure tracing was not enough or there was no oscillation during the recordings and in 3 patients we noticed presence of spontaneous breathing during recordings). Demographics, diagnosis and comorbidities of the patients were given in Table 1. Admission blood gas values: pH: 7.30 ± 0.17, PaO₂: 73 ± 28 mmHg, PaCO₂: 52 ± 21 mmHg, HCO₃: 24 ± 6 mEq, Sat O₂: 87 ± 11%. According to statistical analysis results there were good correlation and agreement and there was no bias between the measurements. Elastance derived method measured PL significantly higher than other formulas (p < 0.05). Respiratory mechanics were presented in Table 2.

3.1 Comparison of elastance derived method with directly measured method

There was a significant difference between the mean values of measurements according to Wilcoxon signed rank test results [13 ± 9 cmH₂O for PL_D and 18 ± 9 cmH₂O for PL_E, (p = 0.014)], and there was a good agreement and there

Table 2 Measurements of the airway and esophageal pressures and derived parameters

	Mean ± SD	Min Max
Esoophageal pressure, P _{es} end-insp plato, cmH ₂ O	10 ± 8	- 4.29
Esoophageal pressure P _{es} end-exp, cmH ₂ O	7 ± 7	- 6.23
Esoophageal pressure, P _{espeak} , cmH ₂ O	9 ± 9	- 4.28
Esoophageal pressure, P _{esplato} , cmH ₂ O	10 ± 8	- 1.5.29
Esoophageal pressure, P _{esexp} , cmH ₂ O	6 ± 7	- 6.3
Esoophageal pressure, P _{es ZEEP} , cmH ₂ O	1.8 ± 4.3	- 9.13
P _{peak} , cmH ₂ O	28 ± 6	17.38
Plato pressure, P _{plat} , cmH ₂ O	22 ± 5	14.32
P _{expiratory} , cmH ₂ O	6 ± 3	0.5 16
Elastance of respiratory system, E _{RS} , cmH ₂ O/L	36.7 ± 13	20.79
Elastance of lung, E _L , cmH ₂ O/L	28.2 ± 17	- 40.65
Elastance of chest wall, E _{CW} , cmH ₂ O/L	10.5 ± 16	- 3.90
E _L /E _{RS} , %	0.75 ± 0.35	- 0.80.1
Inspiratory transpulmonary pressure, PL _D direct method, cmH ₂ O	13 ± 9	- 2.29
Inspiratory transpulmonary pressure PLR released derived method, cmH ₂ O	11.4 ± 9.4	- 4.1.28.7
Inspiratory transpulmonary pressure, elastance derived PL _E , cmH ₂ O	18 ± 9	2.45
PL _{expiratory} , cmH ₂ O, expiratory measurement	0.54 ± 7.7	- 21.12
Mechanical ventilation parameters		
PEEPi, cmH ₂ O	2.6 ± 3.1	0.5–13
Tidal volume, V _T , mL	434 ± 38	354–520
FiO ₂ , %	43 ± 15	40–100
Respiratory rate, rate/min	17 ± 4	12–31
PEEP set, cmH ₂ O	5	5–5

was no bias between the measurements Bias, (regression) in Bland–Altman analysis was: $p: 0.833$.

Agreement (one sample t test):

Mean difference: -3.12 ± 11 , $p: 0.093$, upper confidence limit: $18.44((11 \times 1.96) + (-3.12))$, lower confidence limit: $-18.44(- (11 \times 1.96) - (-3.12))$.

Correlation analysis showed good and significant correlation between the measurements (Spearman correlation analysis: $R: 0.619$, $p: 0.005$).

3.2 Comparison of elastance derived method and relaxed derived method

Since release derived PL (PL_R) calculated only in 26 patients all statistical analysis including Bland–Altman was performed in them.

There was a significant difference between the mean values of measurements ($PL_R 11 \pm 9$, $PL_E 15.2 \pm 10$, $p: 0.005$). In Bland–Altman analysis there was a good agreement and there was no bias between the measurements (Bias (regression): $p: 0.776$).

Agreement (One sample t test): Mean difference: 3.9 ± 10.9 , $p: 0.080$. upper confidence limit: $25.26((10.9 \times 1.96) + (3.9))$ lower confidence limit: $-17.46(- (10.9 \times 1.96) - [3, 9])$.

Correlation analysis showed good and significant correlation between the measurements ($R: 0.615$, $p: 0.002$). Bland–Altman plots of the comparisons were given in Fig. 2.

Accuracy values of the PL_E and PL_R were 79% and 77% respectively when we consider PL_D as gold standard method.

4 Discussion

Our study results showed that there was a good correlation and agreement between the measurements and there was no bias between them, but elastance derived method calculated PL significantly higher than the other two methods. These findings are in line with the results of other studies performed in patients with ARDS [21, 22]. Inspiratory PL is an important parameter to reflect lung overdistension and PL_D is the most frequently used method for this aim. But there is progressively increasing clinical data and debate about the differences between the PL_D and PL_E . Since there is no consensus about which computation method should be used to calculate PL recent literature have measured and presented the results of both measurement method in their studies. Nearly in all of them inspiratory PL calculated with PL_E method is about 5 to 8 cmH_2O higher than the PL_D . In this clinical study we confirmed these results in our ICU patient population with mixed pulmonary mechanical problems. Computation method is important while using PL to set PEEP and tidal volume. Recent studies suggest that

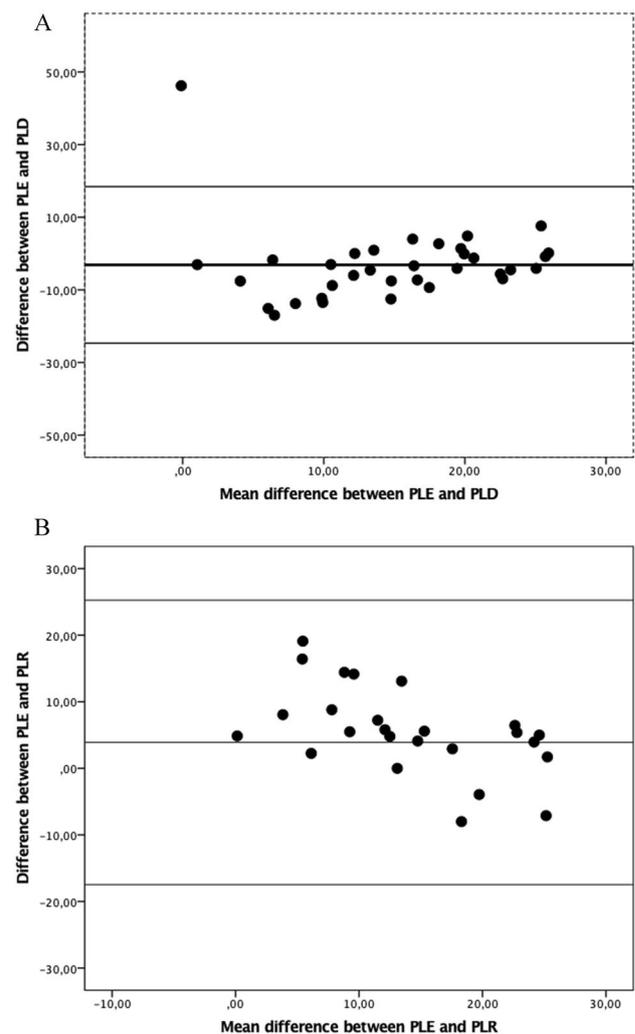


Fig. 2 Comparison of different formulas with Bland–Altman graphic

different formulas may lead different ventilator settings [23]. In a recent study comparing obese and nonobese COVID19 patients' respiratory mechanics Mezidi et al. used both inspiratory PL_D and PL_E measurement methods. They found that PL_E measured PL higher than PL_D method in both obese and nonobese patients. At 16 $cm H_2O$ of PEEP, while 71% of non-obese and 0% of obese patients had $PL_D > 20 cm H_2O$, 86% of non-obese and 75% of obese patients had $PL_E > 20 cmH_2O$ [21].

Berges' et al. aimed to compare estimated alveolar distension with measurement of PL_E , during individual PEEP titration using two different targets: P_{plat} 28–30 cmH_2O or positive $PL_{expiratory}$ 0–5 cmH_2O [22]. They also monitored overdistension using PL_D method. When they titrated PEEP levels according to EXPRESS protocol, PEEP was titrated on the basis of P_{plat} . Mean PL_E was 20 cmH_2O , and PL_D was significantly lower than PL_E with a mean difference of 8.5 cmH_2O ($p < 0.0001$). With the PL_{expi} protocol, mean

PL_E was 24 cmH₂O, and PL_D was significantly lower than PL_E with a mean of difference of 8.7 cmH₂O ($p < 0.0001$).

One of the possible explanations of why these three different methods give different estimates of PL is that they use different P_{es} values to calculate PL. While absolute inspiratory P_{es} value is used to calculate PL_D , delta P_{es} (difference P_{es} end-inspiratory and P_{es} end-expiratory) is used to calculate PL_E . On the other hand PL_R uses P_{es} measured at P_{ZEEP} at atmospheric pressure during release maneuver. This method requires disconnection of patient from the ventilator [13, 14]. As previously shown by Pelosi et al. and recently confirmed by experimental and clinical studies there is not a single P_{pl} value among the thorax [24–28]. In these studies authors placed pleural catheters to the dependent and nondependent lung regions and compared P_{pl} with the P_{es} and showed that the static P_{pl} increases from nondependent to dependent regions in supine position, creating a vertical pressure gradient. In Tilmonts' study PL values calculated using P_{es} were close to those obtained from the dependent pleural catheter but higher than those obtained from the nondependent pleural catheter both during expiration and inspiration in ventilated lung transplant recipients. During controlled ventilation, the absolute value of P_{es} was higher than the P_{pl} of nondependent lung regions and could therefore underestimate the highest level of lung stress in nondependent lung regions. In addition, the elastance-derived method seemed useful to prevent this pitfall. Results of these studies suggest that the direct approach gives a better estimation of expiratory and inspiratory PL of the dependent lung, therefore possibly useful to set PEEP, while the elastances ratio approach better estimates the inspiratory PL of the nondependent lung so that it should be used to set the appropriate tidal volume (or pressure support) and as a target to reduce VILI.

Therefore recent studies suggest that both approaches may give results for clinical application but with different meanings.

Talmor and colleagues, assuming that P_{es} equals the P_{pl} , proposed to set PEEP as to reach a positive P_L at end expiration. The rationale of this approach is that being the P_{es} equal to P_{pl} , a negative PL corresponds to a collapsed lung. Setting PEEP values according to inspiratory PL_D they avoided overdistention of lung. This approach was proposed and tested in humans and resulted in better compliance and oxygenation, but not in a decreased mortality when compared to the traditional FiO₂/PEEP table approach [3]. A recent randomized controlled trial was unable to show any survival benefit using this approach compared to an empirical high PEEP-FiO₂ titration table in patients with moderate to severe ARDS [20].

To eliminate the influence of the mediastinal weight and assuming that its influence is constant throughout the respiratory cycle, Gattinoni et al. proposed PL_E method [2, 29].

This method assumes that the lung and respiratory system pressure–volume curves are linear in the range of PEEP and the tidal volume used in the clinical setting. The reason why this method does not use absolute P_{es} value to calculate P_L is that while delta P_{pl} equals to delta P_{es} , absolute P_{pl} is not equal to absolute P_{es} in all lung regions. This method estimates the portion of P_{aw} that is spent to inflate the lungs, and the portion that is required to move the chest wall, based on the relative contribution of E_L and E_{CW} to E_{RS} . In general 30 cmH₂O of P_{pl} in a general ARDS population is associated with a PL of approximately 21 cmH₂O, being the average E_L/E_{RS} equal to 0.7. On the other hand, the E_{CW}/E_{RS} is not a fixed value, but may vary in this population from 0.2 to 0.8. For this reason, the resulting PL may range from approximately 10 to 28 cmH₂O after applying 30 cmH₂O to the whole respiratory system.

In another study Chiumello et al. compared 3 measurement methods of PL and found PL_E and PL_R very similar in patients with ARDS. They showed that, there was a good correlation between the end-inspiratory PL calculated with the PL_E and the release-derived methods. The mean PL_E and PL_R was 14.4 ± 3.7 and 14.4 ± 3.8 cm H₂O at 5 cmH₂O of PEEP and 21.8 ± 5.1 and 21.8 ± 4.9 cmH₂O at 15 cmH₂O of PEEP, respectively [13]. In contrast to this study we found PL_E significantly higher than PL_R in our study.

Approximately 30% of our study population had obesity and intraabdominal hypertension (IAH) in our study. Obesity increases baseline IAP of approximately 9–15 mmHg. Obese patients have reduced lung volume with increased atelectasis, lung and chest wall compliance. Based on previous studies' data, Pelosi et al. found a relationship between IAP and chest wall elastance. They recommended that PL_D measurement should be required if IAP is higher than 12 mmHg or if chest wall elastance is likely to be increased for other reasons [30, 31].

Assessment of PL seems important to understand the effect of different ventilator settings and to optimize interventions. Therefore before use it routinely for assessment of lung overdistention it is important to know how to measure it and which upper limit should be used needs to be determined and standardized. Despite all three methods reflect lung stress there are different reports giving acceptable upper limit of PL. In general limiting PL_E lower than 25 cmH₂O and PL_D lower than 20 mmHg have been proposed in ARDS patients [5, 6].

5 Limitations of the study

Major limitation of our study is limited number of patients. Having more patients and to compare different calculation methods in patients with different pathologies such as obesity chest wall problems would have been more informative.

6 Conclusion

Since targeting an inaccurate PL could be potentially dangerous as it may lead to over- or underinflation of the lung and thus could cause VILI and every method for the estimation of PL is based on assumptions, the choice of which method and threshold value to use should be standardized. These issues need to be supported by further trials.

Declarations

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval The study was approved by the ethics committee of the Gazi University Faculty of Medicine (28.12.2015/166).

Informed consent Written informed consent was obtained from all patients.

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