



Early View

Original article

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Esophageal pressure as a surrogate of pleural pressure in mechanically-ventilated patients

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Abstract

Background: Esophageal pressure (P_{es}) is used to approximate pleural pressure (P_{PL}) and therefore to estimate transpulmonary pressure (P_L).

Objectives: We aimed to compare esophageal and regional pleural pressures and to calculate transpulmonary pressures in a prospective physiological study on lung transplant recipients during their stay in the intensive care unit of a tertiary university hospital.

Methods: Lung transplant recipients receiving invasive mechanical ventilation and monitored by esophageal manometry and dependent and non-dependent pleural catheters were investigated during the post-operative period. We performed simultaneous short time measurements and recordings of esophageal manometry and pleural pressures. Expiratory and inspiratory P_L were computed by subtracting regional P_{PL} or P_{es} from airway pressure; inspiratory P_L was also calculated with the elastance ratio method.

Results: Sixteen patients were included. Among them, 14 were analyzed. Esophageal pressures correlated with dependent and non-dependent pleural pressures during expiration, respectively $R^2=0.71$, $p=0.005$ and $R^2=0.77$, $p=0.001$ and during inspiration, respectively, $R^2=0.66$ for both (respectively $p=0.01$ and $p=0.014$). P_L calculated using P_{es}

were close to those obtained from the dependent pleural catheter but higher than those obtained from the non-dependent pleural catheter both during expiration and inspiration.

Conclusion: In ventilated lung transplant recipients, esophageal manometry is well correlated to pleural pressure. Absolute value of P_{es} is higher than pleural pressure of non-dependent lung regions and could therefore underestimate the highest level of lung stress in these at high risk of overinflation.

Keywords : Pleural pressure; esophageal pressure; transpulmonary pressure; dependent and non-dependent lung regions; lung transplant recipient.

Introduction

Mechanical ventilation for Acute Respiratory Distress Syndrome (ARDS) is still challenging. Recent guidelines have established strong recommendations for using low tidal volumes (V_t) (4-8 ml/kg predicted bodyweight) and limiting plateau pressure (P_{plat}) (1). Concerning the level of positive end expiratory pressure (PEEP) to apply, there is no well-established recommendation notably to use high level of PEEP for patients with the most severe ARDS. Based on a previous pilot study (2), some experts recommend to set PEEP using esophageal manometry by targeting the transpulmonary plateau pressure. Esophageal pressure (P_{es}) is used since decades by physiologists as a surrogate of pleural pressure (P_{PL}) measurement and allows the calculation of the true lung distending pressure, the so-called transpulmonary pressure, $P_L = P_{aw}$ minus P_{es} (3). However, there is controversies about using the absolute value of P_{es} , and some authors recommend to consider the tidal variation of esophageal pressure which allow the calculation of the ratio of the elastance of the chest wall to the respiratory system (4).

Recently, in a ventilated lung-injured pig model and a human-cadaver ventilated model, Dr Yoshida et al. have conciliated these two theories through comparisons of dependent and

non-dependent pleural pressures to esophageal pressure (3). The main result of this latter study is that P_{es} accurately estimates the dependent pleural pressure both at inspiratory and expiratory pressures and that elastance derived inspiratory transpulmonary pressure accurately estimates the non-dependent inspiratory transpulmonary pressure.

Therefore, the objective of this study was to compare the P_{es} with dependent and non-dependent pleural pressures in lung transplanted recipients receiving invasive mechanical ventilation during the post-operative period. Our hypothesis is that transpulmonary pressure calculated with the P_{es} could underestimate the regional P_L of the non-dependent lung.

Methods

Study design, setting and participants

This study was registered in the clinical trial.gov database on June 7th 2017 as NCT03179644 and approved by the ethical committee (Comité de Protection des Personnes Sud Méditerranée, as 2016-A00567-44). This study was conducted in the North University Hospital medical ICU, Marseille, France. According to the French legislation, all patients gave their written informed consent to participate.

Patient were included if they fulfilled the following inclusion criteria: age \geq 18 years admitted in the ICU after a double-lung transplantation and mechanically ventilated. Exclusion criteria were: age $<$ 18 years, pregnancy or breast feeding, lack of medical insurance, deprivation of liberty by a judicial or administrative decision, those hospitalized without consent, single lung transplantation and contra-indication to placement of a nasogastric tube (esophageal varices, esophageal cancer, surgery of the esophagus of less than 1 year). Patients were not included in case of admission in the ICU with open chest after surgery and/or high flow air leaks ($>$ 10% of inspired volume) or if they had systemic sclerosis with esophageal involvement.

Pleural Pressures Measurements

Before chest closure, the thoracic surgeon introduced the multi-holes pleural catheters (Pleurocath, plastimed Inc, France) along the thoracic drains under direct view. The non-dependent catheters were positioned at the surface of the anterior visceral pleura, dependent catheters were positioned at the surface of the posterior visceral pleura (**Supplementary Figure 1**). According to surgical considerations, two or four pleural catheters were positioned on the right and/or left side, at least one to measure the dependent pleural pressure and one to measure the non-dependent pleural pressure *per* patient. Before measurement, we verified catheter emptiness with 5 ml of air. Chest tubes were then clamped during measurements. Pleural catheters were thereafter connected to a pressure port of the Fluxmed monitor, (MBMED Inc, Argentina). The good transmission of pleural pressure was assessed by an occlusion test as shown in **Figure 2**. We performed 3 to 5 minutes recordings for each pleural tracings during the first 48 hours post-operative.

Esophageal Pressures Measurements

An esophageal balloon catheter (NutriventTM, Sidam, Mirandola, Italy) was inserted and inflated with a minimal, non-stress volume (2-3 ml) of air as recommended (4). The adequate position of the balloon in the lower part of the esophagus was confirmed by presence of cardiac artifacts on the esophageal curve and a positive occlusion test (expiratory hold on the ventilator) in passive conditions with gentle chest compression (5). Esophageal pressure was recorded by the same device used for pleural pressure recordings. The occlusion test was considered as positive if the relationship between ΔP_{PL} and ΔP_{aw} should yield a slope of 1.0 ± 0.2 cm H₂O, as well as between ΔP_{es} and ΔP_{aw} . In case of negative test, tracings and measurements were not analyzed. Measurements were performed in static condition (zero flow) during an end inspiratory occlusion pause of 2 sec allowing the measurement of

respectively Pplat and inspiratory P_{es} ($P_{es, insp}$) and following an end expiratory occlusion pause of 5 sec allowing the measurement of respectively total PEEP ($PEEP_{tot}$) and expiratory P_{es} ($P_{es, exp}$).

Definitions and Calculations

The following formula were used for assessment of transpulmonary pressures (P_L).

Inspiratory transpulmonary pressure ($P_{L, insp}$), using esophageal pressure as $P_{L, insp, es} = P_{plat} - P_{es, insp}$, or using direct measurement of P_{PL} in non-dependent lung, as $P_{L, ND, insp} = P_{plat} - P_{PL, ND, insp}$ and in dependent lung, as $P_{L, D, insp} = P_{plat} - P_{PL, D, insp}$.

Conversely, expiratory transpulmonary pressure ($P_{L, exp}$) were determined using esophageal pressure as $P_{L, exp, es} = PEEP_{tot} - P_{es, exp}$, or using direct measurement of P_{PL} in non-dependent lung, as $P_{L, ND, exp} = PEEP_{tot} - P_{PL, ND, exp}$ and in dependent lung, as $P_{L, D, exp} = PEEP_{tot} - P_{PL, D, exp}$.

Additionally, $P_{L, insp}$ was also calculated from elastance ratio of chest wall to respiratory system (6), as $P_{L, insp, ER} = P_{plat} - [P_{plat} \times EL_{CW} / EL_{RS}]$. Accordingly, respiratory system elastance (EL_{RS}) = $(P_{plat} - PEEP_{tot}) / V_t$ and, chest wall elastance (EL_{CW}) = $(P_{es, insp} - P_{es, exp}) / V_t$. All pressures were expressed in cm of water (cmH₂O).

Statistical analysis

As it is an exploratory physiological study, no statistical power calculation was anticipated. However, the ethical committee allowed to enrol a maximum of 45 patients during a two years period. All presented results are part of the primary analysis of the data. All statistics were performed by two-tailed tests. Continuous variables were reported as the mean \pm sd or median (inter-quartiles ranges) as appropriate. Comparisons were performed by Student's t-test or by Mann Whitney test as appropriate. Categorical variables were expressed as the absolute value and percentage. Comparisons were performed by Chi-square test. Normality of the distribution of variables were tested by the Kolmogorov-Smirnov and the Shapiro-Wilk

tests. Correlations were performed with Pearson correlation test with further Bland and Altman analysis for each correlation. A two-way repeated-measures analysis of variance (ANOVA) was performed to compare transpulmonary pressures at end expiration and end inspiration according to the modality of calculation and to the level of applied PEEP. The normality of the distribution of the residuals, the assumption of sphericity and the interaction between transpulmonary pressures and PEEP were checked. Intra-group differences were evaluated by *post hoc* Bonferroni pairwise multiple comparisons. A *p* value < 0.05 was retained as significant. All statistics and figures were performed with the SPSS 20.0 package (SPSS, Chicago, IL, USA).

Results

Patients and measurements

Twenty two lung transplant recipients gave their informed consent before surgery (**see flow chart as Figure 1**). Six patients were secondary excluded. Sixteen lung transplant recipients were recorded. Two additional patients were not analyzed because of negative occlusion test (correlations between ΔP_{es} and ΔP_{aw} and/or ΔP_{PL} and ΔP_{aw} < 0.8). Main characteristics of the fourteen remaining patients are displayed in **Table 1**. An illustrative tracing of pressures, flow and volume during an occlusion test with chest compression is provided in **Figure 2**. Fifty percent of patients were assisted by veno-venous extracorporeal membrane oxygenation (vvECMO) at ICU admission. All measurements were performed while patients were sedated and mechanically ventilated in volume assisted controlled mode with a range of PEEP between 8 and 14 cmH₂O without spontaneous breathing effort. Among the 14 patients, 4 had daily serial measurements totalizing 24 measurements.

Correlations between esophageal and pleural pressures

Occlusions tests yield 0.95 ± 0.05 for $\Delta P_{es}/\Delta P_{aw}$ and 0.94 ± 0.06 for $\Delta P_{PL}/\Delta P_{aw}$. Dependent and non-dependent expiratory pleural pressures were significantly correlated with expiratory esophageal pressure (respectively $R^2=0.71$ and $R^2=0.77$, $p<0.01$ for both) (**Figure 3, panel A**). Dependent and non-dependent inspiratory pleural pressures were significantly correlated with inspiratory esophageal pressure, respectively $R^2=0.66$ for each ($p<0.05$) (**Figure 3, panel B**). Esophageal pressure was always found higher than non-dependent pleural pressure. During expiration time, mean difference between esophageal pressure and dependent pleural pressure was 0.48 ± 2.87 cmH₂O and 5.25 ± 2.51 cmH₂O between esophageal pressure and nondependent pleural pressure (Figure 3, panel A). During inspiration time, mean difference between esophageal pressure and dependent pleural pressure was 0.98 ± 2.90 cmH₂O and 6.09 ± 2.90 cmH₂O between esophageal pressure and non-dependent pleural pressure. The mean difference between dependent pleural pressure and non-dependent pleural pressure was 4.76 ± 2.94 cmH₂O at expiratory time and 5.38 ± 2.11 cmH₂O at inspiratory time.

Correlations between transpulmonary pressures

Correlations and Bland and Altman analysis between inspiratory transpulmonary pressures according the four ways of calculation are presented in **Figure 4 (panel A)**. Inspiratory P_L computed from esophageal pressure were better correlated with inspiratory P_L calculated from dependent and non-dependent pleural pressures than those calculated from the elastance ratio method (6) ($R^2 = 0.604$, $R^2 = 0.629$ and $R^2 = 0.45$, $p<0.05$ for all, respectively). However, the estimated bias was higher between $P_{L, insp, es}$ and $P_{L, ND, insp}$ than between $P_{L, insp, es}$ and $P_{L, D, insp}$ (-6 ± 3.94 and -1.61 ± 3.62 cm H₂O respectively). Correlations and Bland and Altman analysis between expiratory transpulmonary pressures according the three ways of calculation are presented in **Figure 4 (panel B)**. Expiratory P_L computed from esophageal pressure were modestly correlated with expiratory P_L calculated from dependent and non-dependent pleural

pressures ($R^2=0.479$ and $R^2 = 0.531$, $p<0.02$, respectively). However, the agreement was better between $P_{L, exp, es}$ and $P_{L, D, exp}$ than between $P_{L, exp, es}$ and $P_{L, ND, exp}$ (estimated bias -1.34 ± 3.32 and -5.55 ± 3.36 cmH₂O respectively).

Relationship between expiratory transpulmonary pressures at different PEEP levels

Expiratory transpulmonary pressures calculated using P_{es} were close to those obtained from the dependent pleural catheter (**Figure 5- panel A**). Expiratory transpulmonary pressure calculated with non-dependent pleural catheter ($P_{L, ND, exp}$) were higher than those calculated from both dependent catheter ($P_{L, D, exp}$) and esophageal pressure ($P_{L, exp, es}$) whatever the PEEP level. We also found a significant interaction between PEEP and $P_{L, exp}$ ($R^2=0.301$, $p=0.02$).

Relationship between inspiratory transpulmonary pressures at different PEEP levels

Inspiratory transpulmonary pressures calculated using P_{es} was close to those directly measured by the dependent pleural catheter (**Figure 5- panel B**). Inspiratory transpulmonary pressure calculated from the elastance ratio of chest wall to respiratory system ($P_{L, insp, ER}$) was also close to those measured using the non-dependent pleural catheter ($P_{L, ND, insp}$). In our model, $P_{L, insp, es}$ underestimates the true regional transpulmonary pressure of the non-dependent lung region ($P_{L, ND, insp}$). We did not find interaction between PEEP and $P_{L, insp}$ ($R^2=0.132$, $p=0.203$).

Discussion

In this mechanically ventilated *in vivo* human model, P_{es} is close to the pleural pressures of the dependent lung region. However, we found overestimation by P_{es} of the non-dependent lung region pleural pressures. Therefore, the limitation of inspiratory lung stress using P_{es} may lead to underestimate the lung stress in non-dependent lung regions. Rather, inspiratory P_L calculated with the elastance ratio ($P_{L, insp, ER}$) may reflect local lung stress in non-dependent lung regions which are usually the overinflated lung regions.

From previous clinical and experimental studies, we know that 1/ because of the weight of the heart and of the increase of the gravitational gradient of pleural pressure during ARDS, P_{es} is higher in supine patient ventilated for ARDS than those of non-ventilated healthy subject in upright position(2,7,8) 2/ from experimental study in dogs (9), and recently in man (10), it was demonstrated that absolute pleural pressures are approximately 7 cmH₂O lower than P_{es} in the non-dependent regions and 5 cmH₂O higher in the dependent regions at low intrathoracic pressure. Therefore, some authors have proposed to apply a correction subtraction between 2.5 to 5 cmH₂O to the actual measured esophageal pressure to calculate the transpulmonary pressure (8,9,11). However, the utility of a fixed correction of absolute transpulmonary pressure is still debated (12,13).

An experimental previous study (3) has demonstrated that in anesthetized pigs and human cadavers, 1/ P_{es} was midway between P_{PL} in dependent region and P_{PL} in non-dependent region and 2/ elastance derived transpulmonary pressure matched the directly measured transpulmonary pressure from non-dependent regions.

In addition, Terzi et al.(14) showed in a ventilated pig model that in supine position, mean difference between P_{es} and $P_{L,D}$ was 2.2 cmH₂O and 7.2 cmH₂O between P_{es} and $P_{L,ND}$ at 10cm H₂O of PEEP. Interestingly, whereas prone position did not modify gradient between P_{es} and $P_{L,D}$, the gradient between P_{es} and $P_{L,ND}$ decreased to 1.8 cmH₂O.

Pasticci et al.(10) have recently investigated pleural pressures in human, through the chest tube on the surgery side immediately after lung resection of the non-dependent lung region in lateral and supine positions. The main finding of the study was that esophageal pressures was 7.3 ± 2.8 cmH₂O higher than non-dependent pleural pressure pleural pressures in supine position. But, because of change of pleural pressure induced an identical change in esophageal pressure, the transpulmonary pressures calculated with the elastance ratio

methods were perfectly correlated.

Therefore, the principal strength of our study is to confirm and duplicate in a human *in vivo* setting, results from previous experimental and clinical studies (3,10,14) with the unique characteristic to investigate simultaneously dependent, non-dependent pleural pressures and esophageal pressure.

Minimal discrepancies could be explained by some differences between the models. First, anatomy of the esophagus of pig and human are different with a more posterior location in pig. Second, different cardiac and vascular filling pressures may explain differences in absolute value of esophageal pressure observed in lung transplant recipients and cadavers.

Third, the pleural pressure sensors were different.

Despite some differences between our model and previous experimental models (animal and cadaver), they also share some common results. In the supine position, the dorsal-to-ventral pleural gradient from dependent to non-dependent lung region was 5.0 IQR (2.7-6.4) cm H₂O at inspiration and 4.4 IQR (1.9-5.6) at expiration in our study which is very close from those measured in pigs (median 4.4 IQR (2.4-6.8) cmH₂O) (14) but lower to those measured in cadavers (n=3, 10.0±3.1 cmH₂O) (3). In this latter experiment, despite the “Thiel method” to restore elasticity of the tissues, it is possible that the model affects chest wall recoil force as compared with human.

The elastance derived method to assess transpulmonary pressure ($P_{L, \text{insp}, ER}$) found very close values than those directly measured by $P_{L, ND, \text{insp}}$. These findings are concordant with experimental results and therefore suggesting that $P_{L, \text{insp}, ER}$ could be a valuable target to prevent regional stress and strain of the non-dependent lung regions (3).

There are several limitations to the present study. First, we used a very specific *in vivo* model of mechanically ventilated patients with some of them presenting acute lung injury following lung transplantation (primary graft dysfunction). Second, after open chest surgery, presence of chest tubes, even clamped with no vacuum, may have created some artifacts in the pleural pressure signal. Third, we used common pleural catheter to measure pleural pressure and not specific flat balloon pleural sensors which has only been used only for animal studies so far. However, this was the only device allowed by the French safety drug administration for the study.

Finally, even if esophageal pressures were well correlated with pleural pressures, we found a significant bias of agreement between esophageal pressures and non-dependent pleural pressures of 5.25 ± 2.51 cmH₂O at expiration time and 6.09 ± 2.90 cmH₂O at inspiration time. Of note, a non-inferior bias of agreement of 7.2 ± 5.56 cmH₂O was also reported in a pig model under strict experimental conditions (14).

Although of potential clinical interest, esophageal manometry is still very underused in clinical practice in ARDS patients (0.8% in the cohort of all ARDS patients in the LUNG SAFE study and 1.2% for severe ARDS patients)(15). Recently, the largest trial (EPVent-2 study) using esophageal manometry in ARDS patients (16) has failed to demonstrate outcome benefit with targeting the expiratory transpulmonary pressure as compared with a strategy of high PEEP based on a PEEP-FiO₂ table.

Esophageal manometry may be still of clinical interest in specific ARDS clinical vignettes notably when abdominal or chest wall elastance is increased (17) or unrecognized harmful strong respiratory efforts (18,19). Esophageal manometry remains also useful to diagnose patient – ventilator asynchrony which may worsen the outcome (20–22).

In conclusion, in ventilated lung transplant recipients, esophageal manometry was well correlated to direct measure of pleural pressure with non-specific sensors and absolute value was close to those from dependent lung. During controlled ventilation without respiratory muscles activity, absolute value of P_{es} is higher than pleural pressure of non-dependent lung regions and could therefore underestimate the highest level of lung stress in non-dependent lung regions. In addition, the elastance derived method seems useful to prevent this pitfall.

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References

1. Fan E, Del Sorbo L, Goligher EC, Hodgson CL, Munshi L, Walkey AJ, et al. An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: Mechanical Ventilation in Adult Patients with Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med.* 2017 May;195(9):1253–63.
2. Talmor D, Sarge T, Malhotra A, O'Donnell CR, Ritz R, Lisbon A, et al. Mechanical Ventilation Guided by Esophageal Pressure in Acute Lung Injury. *N Engl J Med.* 2008 Nov 13;359(20):2095–104.

3. Yoshida T, Amato MBP, Grieco DL, Chen L, Lima CAS, Roldan R, et al. Esophageal Manometry and Regional Transpulmonary Pressure in Lung Injury. *American Journal of Respiratory and Critical Care Medicine*. 2018 Apr 15;197(8):1018–26.
4. Mojoli F, Chiumello D, Pozzi M, Algieri I, Bianzina S, Luoni S, et al. Esophageal pressure measurements under different conditions of intrathoracic pressure. An in vitro study of second generation balloon catheters. *MINERVA ANESTESIOLOGICA*. 2015;81(8):10.
5. Baydur A, Behrakis PK, Zin WA, Jaeger M, Milic-Emili J. A Simple Method for Assessing the Validity of the Esophageal Balloon Technique. *American Review of Respiratory Disease*. 1982; 4.
6. Gattinoni L, Chiumello D, Carlesso E, Valenza F. Bench-to-bedside review: chest wall elastance in acute lung injury/acute respiratory distress syndrome patients. *Crit Care*. 2004 Oct;8(5):350-5. doi: 10.1186/cc2854.
7. Washko GR, O'Donnell CR, Loring SH. Volume-related and volume-independent effects of posture on esophageal and transpulmonary pressures in healthy subjects. *Journal of Applied Physiology*. 2006 Mar;100(3):753–8.
8. Talmor D, Sarge T, O'Donnell CR, Ritz R, Malhotra A, Lisbon A, et al. Esophageal and transpulmonary pressures in acute respiratory failure*: *Critical Care Medicine*. 2006 May;34(5):1389–94.
9. Milic-Emili G, Petit JM. Relationship between endoesophageal and intrathoracic pressure variations in dog. *Journal of Applied Physiology*. 1959 Jul;14(4):535–7.
10. Pasticci I, Cadringer P, Giosa L, Umbrello M, Formenti P, Macri MM, Busana M, Bonifazi M, Romitti F, Vassalli F, Cressoni M, Quintel M, Chiumello D, Gattinoni L. Determinants of the esophageal-pleural pressure relationship in humans. *J Appl Physiol* (1985). 2020 Jan 1;128(1):78-86.
11. Ranieri VM, Giuliani R, Mascia L, Grasso S, Petruzzelli V, Bruno F, et al. Chest wall and lung contribution to the elastic properties of the respiratory system in patients with chronic obstructive pulmonary disease. *European Respiratory Journal*. 1996 Jun 1;9(6):1232–9.
12. Terragni P, Mascia L, Fanelli V, Biondi-Zoccai G, Ranieri VM. Accuracy of esophageal pressure to assess transpulmonary pressure during mechanical ventilation. *Intensive Care Med*. 2017 Jan;43(1):142–3.
13. Baedorf Kassis E, Loring SH, Talmor D, Terragni P, Mascia L, Ranieri VM. A fixed correction of absolute transpulmonary pressure may not be ideal for clinical use: Discussion on “Accuracy of esophageal pressure to assess transpulmonary pressure during mechanical ventilation.” *Intensive Care Med*. 2017 Sep;43(9):1436–7.
14. N Terzi, S Bayat, N Noury, E Turbil, W Habre, L Argaud, M Cour, B Louis, C, Guérin. Comparison of pleural and esophageal pressure in supine and prone position in a 2 porcine model of acute respiratory distress syndrome. *Journal of Applied Physiology* [Internet]. 2020 [cited 2020 Aug 4];790601 Bytes. Available from: https://figshare.com/articles/Ppl_vs_Pes_supplemental_data/12278342

15. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. *JAMA*. 2016 Feb 23;315(8):788.
16. Beitler JR, Sarge T, Banner-Goodspeed VM, Gong MN, Cook D, Novack V, et al. Effect of Titrating Positive End-Expiratory Pressure (PEEP) With an Esophageal Pressure-Guided Strategy vs an Empirical High PEEP-FIO₂ Strategy on Death and Days Free From Mechanical Ventilation Among Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. *JAMA*. 2019 Mar 5;321(9):846.
17. Quintel M, Pelosi P, Caironi P, Meinhardt JP, Luecke T, Herrmann P, et al. An Increase of Abdominal Pressure Increases Pulmonary Edema in Oleic Acid-induced Lung Injury. *Am J Respir Crit Care Med*. 2004 Feb 15;169(4):534–41.
18. Mauri T, Langer T, Zanella A, Grasselli G, Pesenti A. Extremely high transpulmonary pressure in a spontaneously breathing patient with early severe ARDS on ECMO. *Intensive Care Med*. 2016 Dec;42(12):2101–3.
19. Yoshida T, Torsani V, Gomes S, De Santis RR, Beraldo MA, Costa ELV, et al. Spontaneous Effort Causes Occult Pendelluft during Mechanical Ventilation. *Am J Respir Crit Care Med*. 2013 Dec 15;188(12):1420–7.
20. Thille AW, Rodriguez P, Cabello B, Lellouche F, Brochard L. Patient-ventilator asynchrony during assisted mechanical ventilation. *Intensive Care Med*. 2006 Oct;32(10):1515–22.
21. Blanch L, Villagra A, Sales B, Montanya J, Lucangelo U, Luján M, et al. Asynchronies during mechanical ventilation are associated with mortality. *Intensive Care Med*. 2015 Apr;41(4):633–41.
22. Bourenne J, Guervilly C, Mechat M, Hraiech S, Fraisse M, Bisbal M, et al. Variability of reverse triggering in deeply sedated ARDS patients. *Intensive Care Med*. 2019 May;45(5):725–6.

Figure legends

Figure 1. Flow diagram of the included patients.

Figure 2. Representative tracing of volume, flow, airway, esophageal and non-dependent pleural pressures during an occlusion test. The increase of airway, esophageal and non-

dependent pleural pressures with the same magnitude during the gentle thoracic compression (white arrows) ensure the correct placement of pleural catheter and esophageal balloon.

Figure 3. Correlations and Bland and Altman analysis between pleural pressures and esophageal pressure, at end-expiration (A) and end-inspiration (B). For correlations, the dotted line represents the identity line. Each circle represents a different patient. For Bland and Altman analysis, black solid line and dotted thin lines represent the mean \pm 2SD of the differences. *Abbreviations:* R^2 , Pearson correlation test.

Figure 4. Correlations and Bland and Altman analysis between transpulmonary pressures, during end-inspiration (A) and end-expiration (B). For correlations, the dotted line represents the identity line. Each circle represents a different patient. For Bland and Altman analysis, black solid line and dotted thin lines represent the mean \pm 2SD of the differences.

Abbreviations: R^2 , Pearson correlation test.

Figure 5. Relationship of transpulmonary pressures calculated from esophageal pressure and pleural pressures in mechanically ventilated human lung transplant recipients.

(A) During expiratory time at different PEEP levels, *Abbreviations:* PEEP positive end-expiratory pressure. * $p < 0.05$ compared with P_{es} and dependent catheter by post-hoc Bonferroni test; Box plot represent median and 25th-75th percentile, outliers are represented by empty circles.

(B) During inspiratory time at different PEEP levels. *Abbreviations:* PEEP positive end-expiratory pressure. * $p < 0.05$ compared with P_{es} and dependent catheter by post-hoc Bonferroni test; Box plot represent median and 25th-75th percentile, outliers are represented by empty circles.

Table 1. Characteristics of the patients

Subject number	Age	Gender	SOFA	SAPS 2	Indication for BLT	vvECMO*	Duration of Mechanical Ventilation (days)	ICU length of stay (days)	ICU survival
1	61	F	9	47	COPD	No	4	13	yes
2	61	M	7	55	Fibrosis	Yes	41	50	yes
3	41	M	7	40	Fibrosis	No	3	9	yes
4	69	M	6	39	Fibrosis	No	1	7	yes
5	69	M	8	53	Fibrosis	Yes	8	13	yes
6	65	M	8	34	Fibrosis	Yes	8	14	yes
7	65	M	11	58	Fibrosis	Yes	5	5	no
8	62	M	5	46	Fibrosis	No	5	13	yes
9	64	M	7	39	Fibrosis	No	5	13	yes
10	61	F	11	51	COPD	Yes	90	90	yes
11	53	M	9	48	Fibrosis	Yes	6	10	yes
12	62	F	7	50	COPD	No	43	47	yes
13	64	M	8	47	COPD	Yes	14	14	no
14	64	M	10	52	COPD	No	1	4	yes
Mean±sd	61±7		8±2	47±7			17±25	2±24	

Table 1 (continued). Gas exchanges, mechanical ventilation settings and respiratory system mechanics

Subject number	PaO ₂ /FiO ₂	pH	PaCO ₂	Tidal Volume (mL)	Plateau pressure (cmH ₂ O)	PEEP cmH ₂ O	Driving pressure (cmH ₂ O)	Respiratory System Elastance (cmH ₂ O/L)	Chest Wall Elastance (cmH ₂ O/L)	Elastance ratio
1	60	7.35	40	340	28	12	16	47	7	.15
2	346	7.26	30	270	21	10	11	41	21	.51
3	184	7.41	41	334	22	10	12	36	17	.47
4	388	7.39	35	443	22	8	14	32	8	.25
5	200	7.29	34	250	27	14	13	52	11	.21
6	157	7.49	33	383	25	10	15	39	3	.08
7	65	7.30	50	284	31	15	16	56	9	.16
8	150	7.30	78	358	26	10	16	44	4	.09
9	160	7.34	49	417	16	5	11	26	6	.23
10	90	7,36	39	200	24	10	14	70	18	.26
11	126	7.30	37	222	26	14	12	54	8	.15
12	140	7,36	41	321	29	14	15	47	5	.11
13	225	7.42	32	460	23	14	9	20	12	.60
14	250	7.38	36	400	25	12	13	32	8	.25

Mean±sd	181±96	7.35±0.06	41±12	334±81	25±4	11±3	13±2	42±13	10±5	.25±.16
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F, female gender; M, male gender; SOFA, sepsis-related organ failure assessment score at inclusion; SAPS 2, simplified acute physiologic score 2 at inclusion; BLT, bilateral lung transplantation; vvECMO, veno venous extracorporeal membrane oxygenation; ICU, intensive care unit; PEEP, positive end expiratory pressure; sd, standard deviation.

* At ICU admission.

Figure 1. Flow diagram of the included patients.

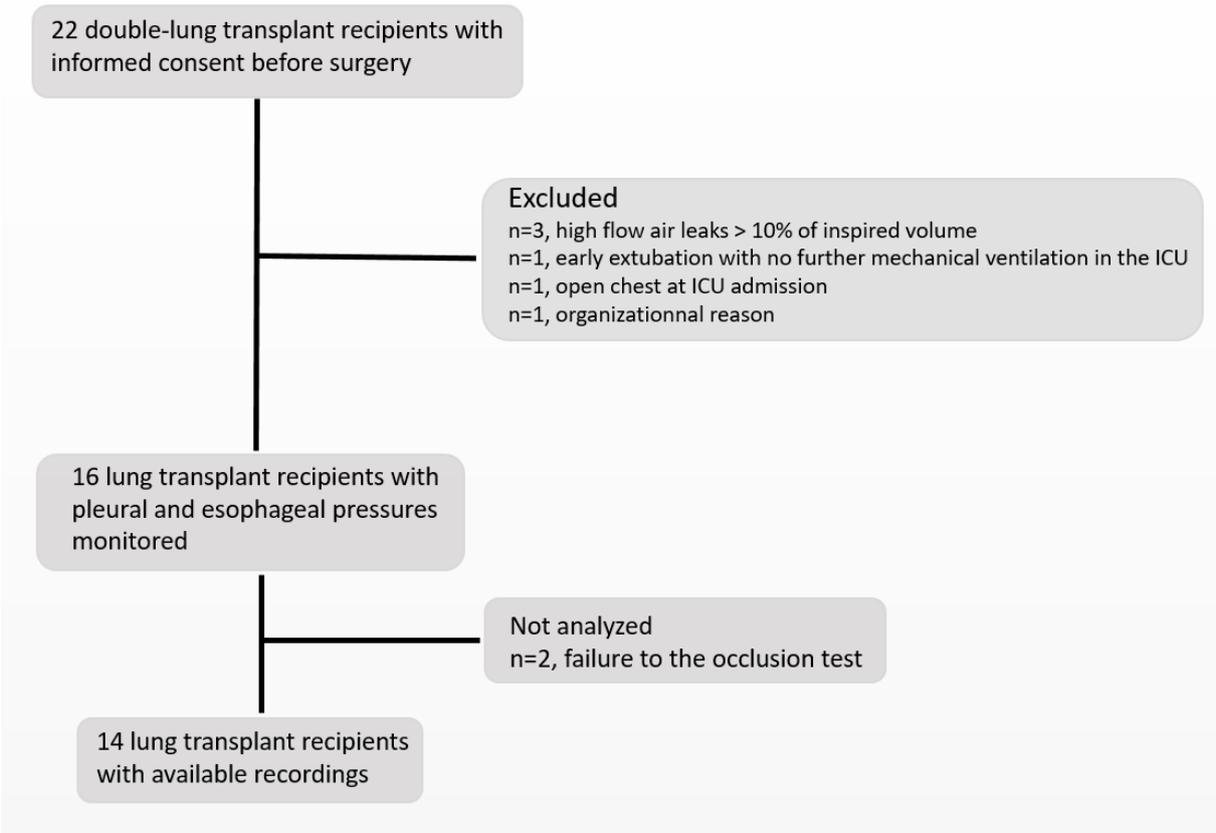


Figure 2. Representative tracing of volume, flow, airway, esophageal and non-dependent pleural pressures during an occlusion test (white arrows).

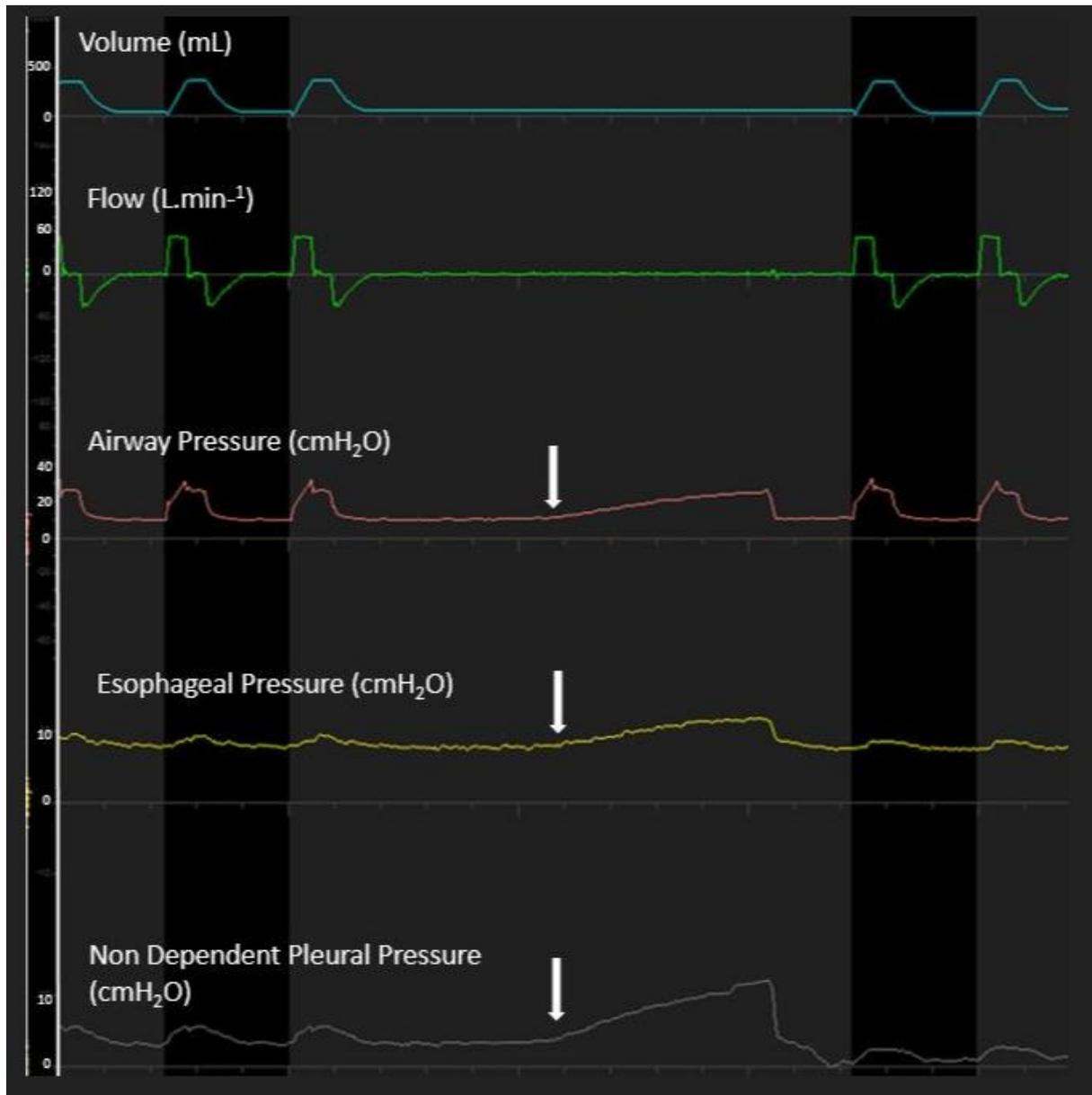


Figure 3

(A)

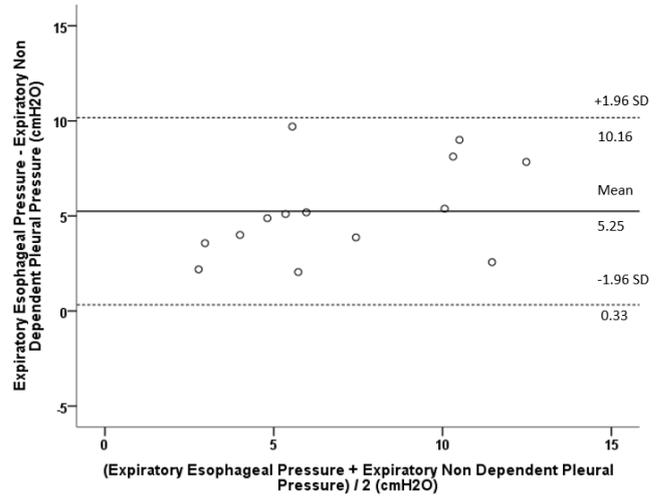
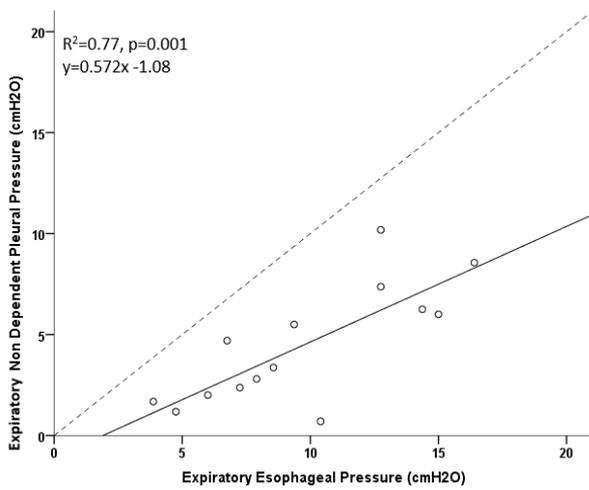
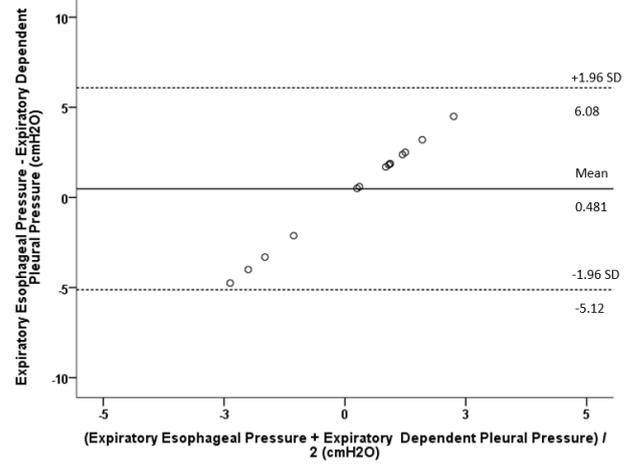
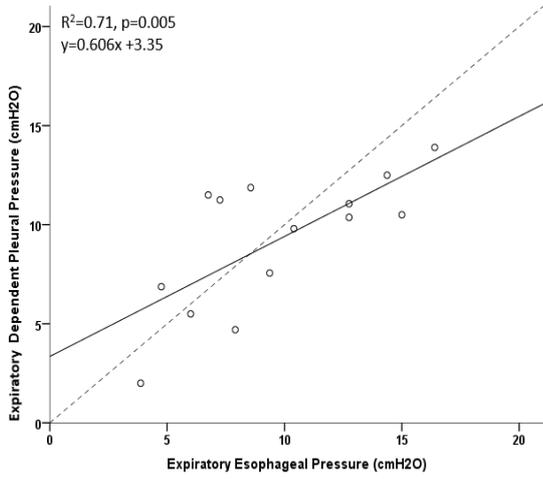


Figure 3

(B)

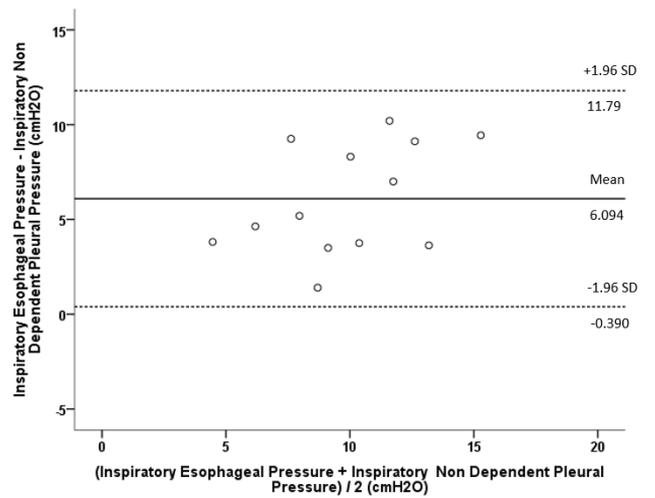
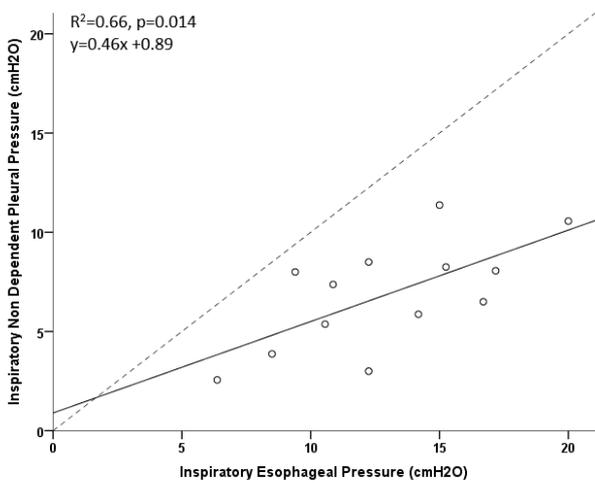
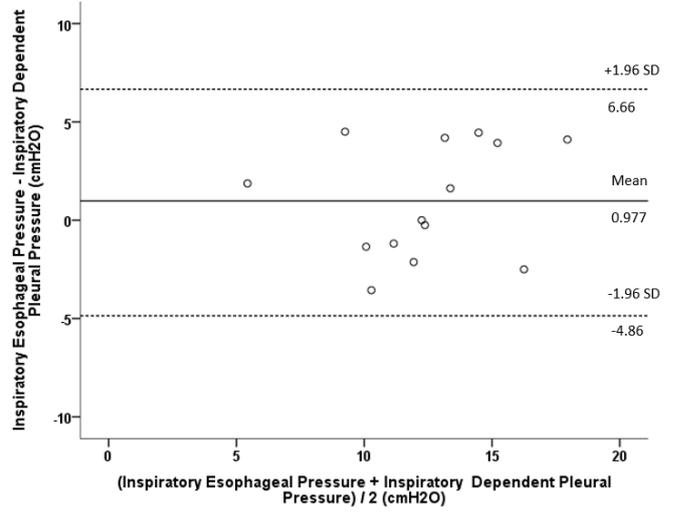
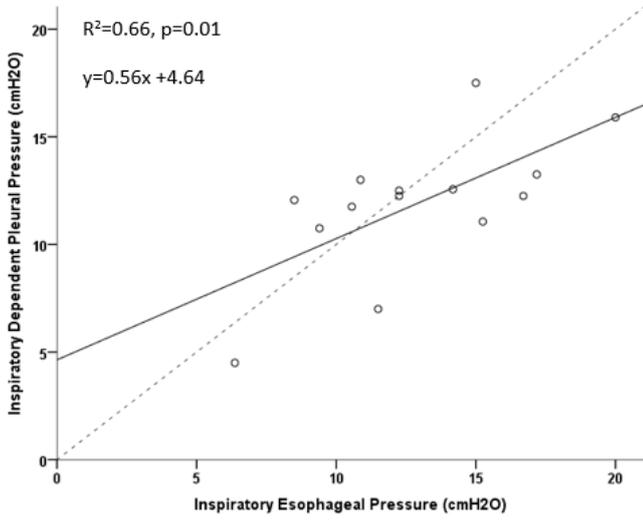
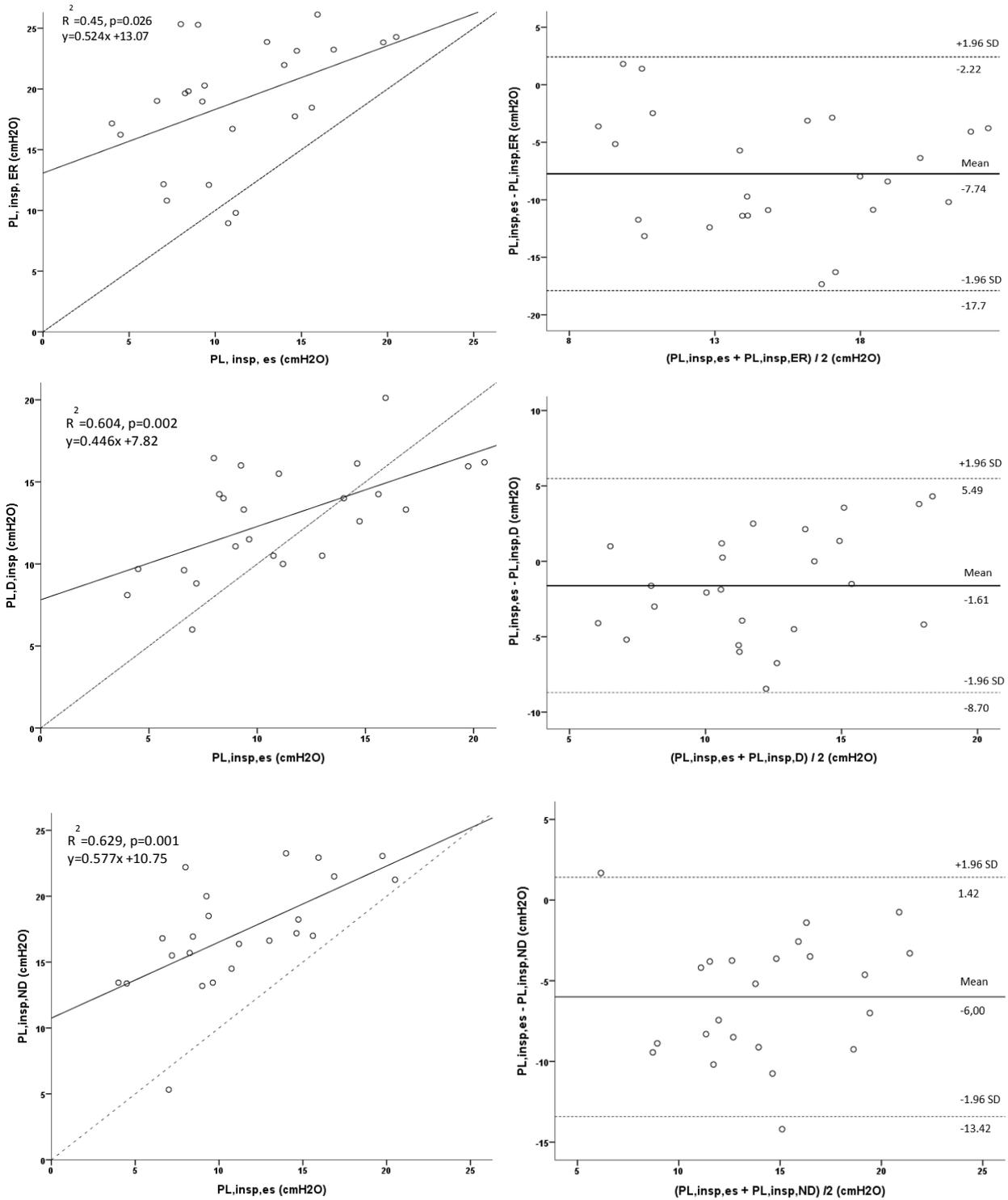


Figure 4: Correlations and Bland and Altman analysis between transpulmonary pressures

Panel A: During inspiratory time



Panel B: During expiratory time

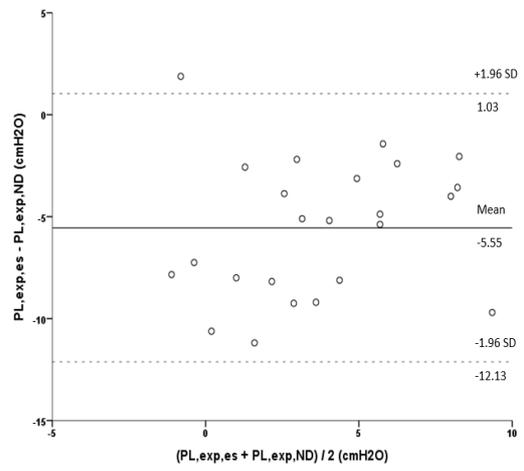
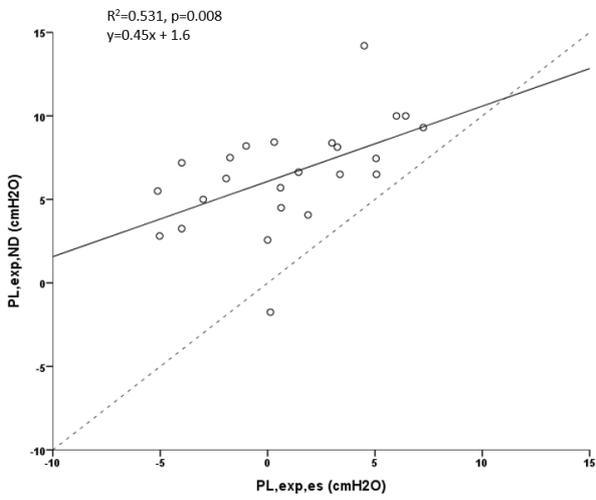
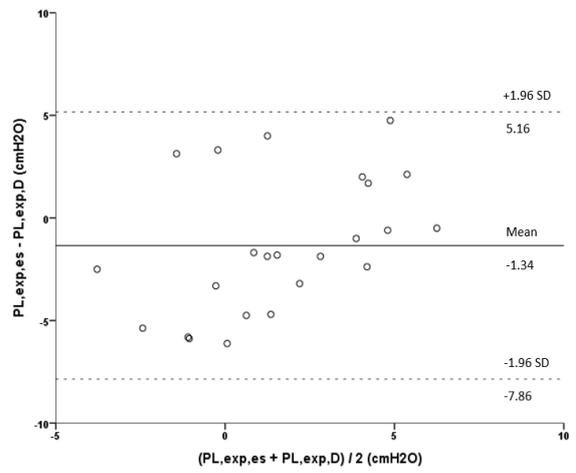
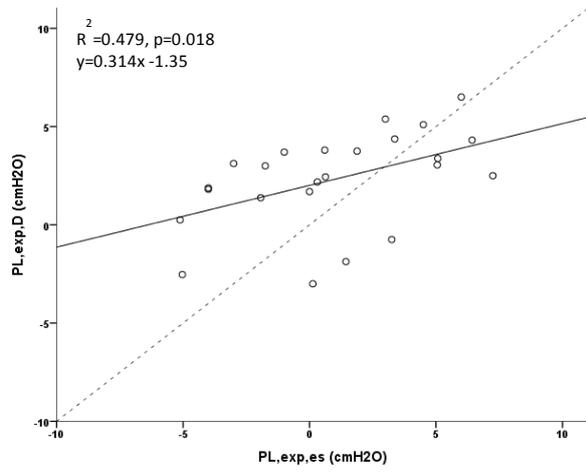
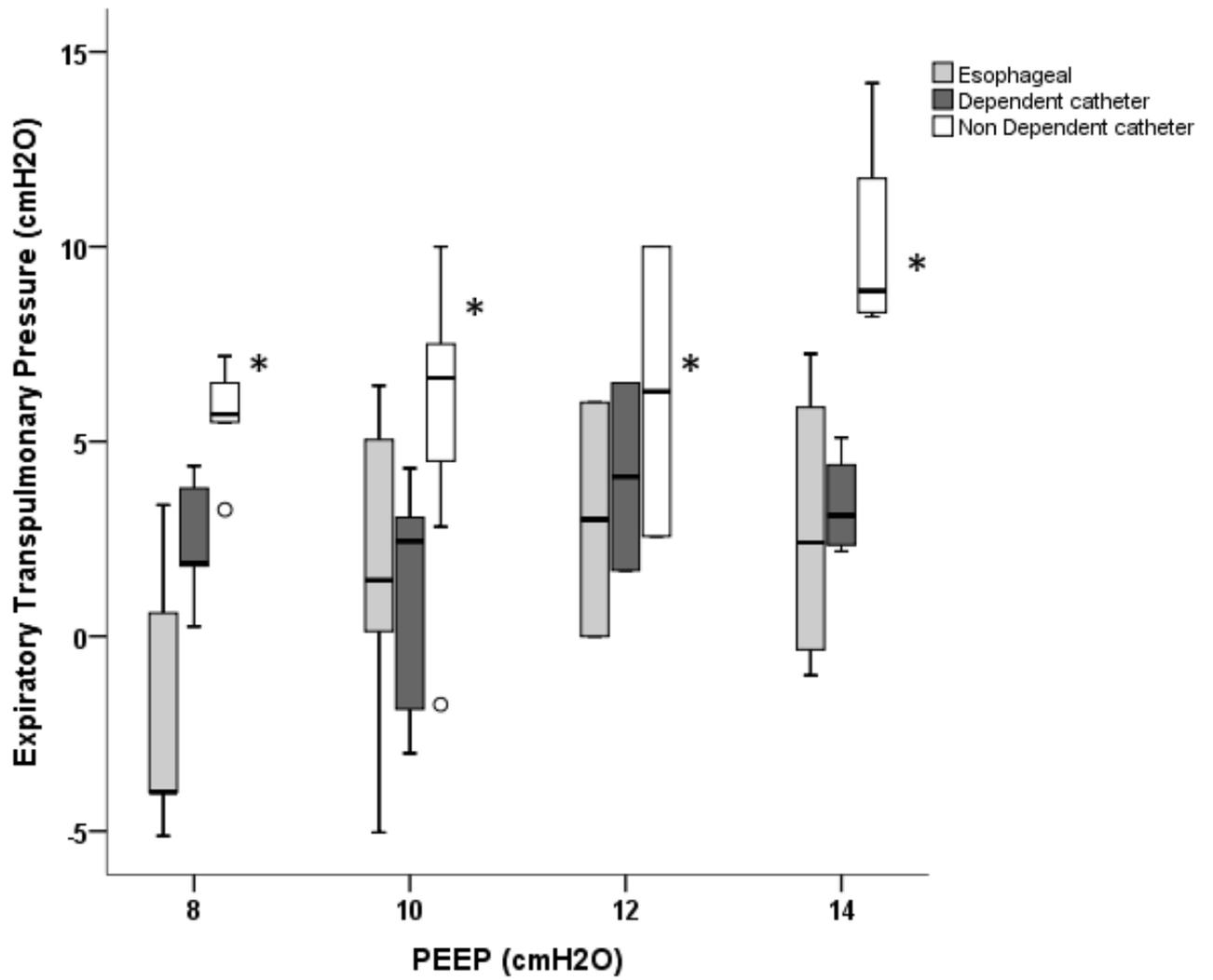


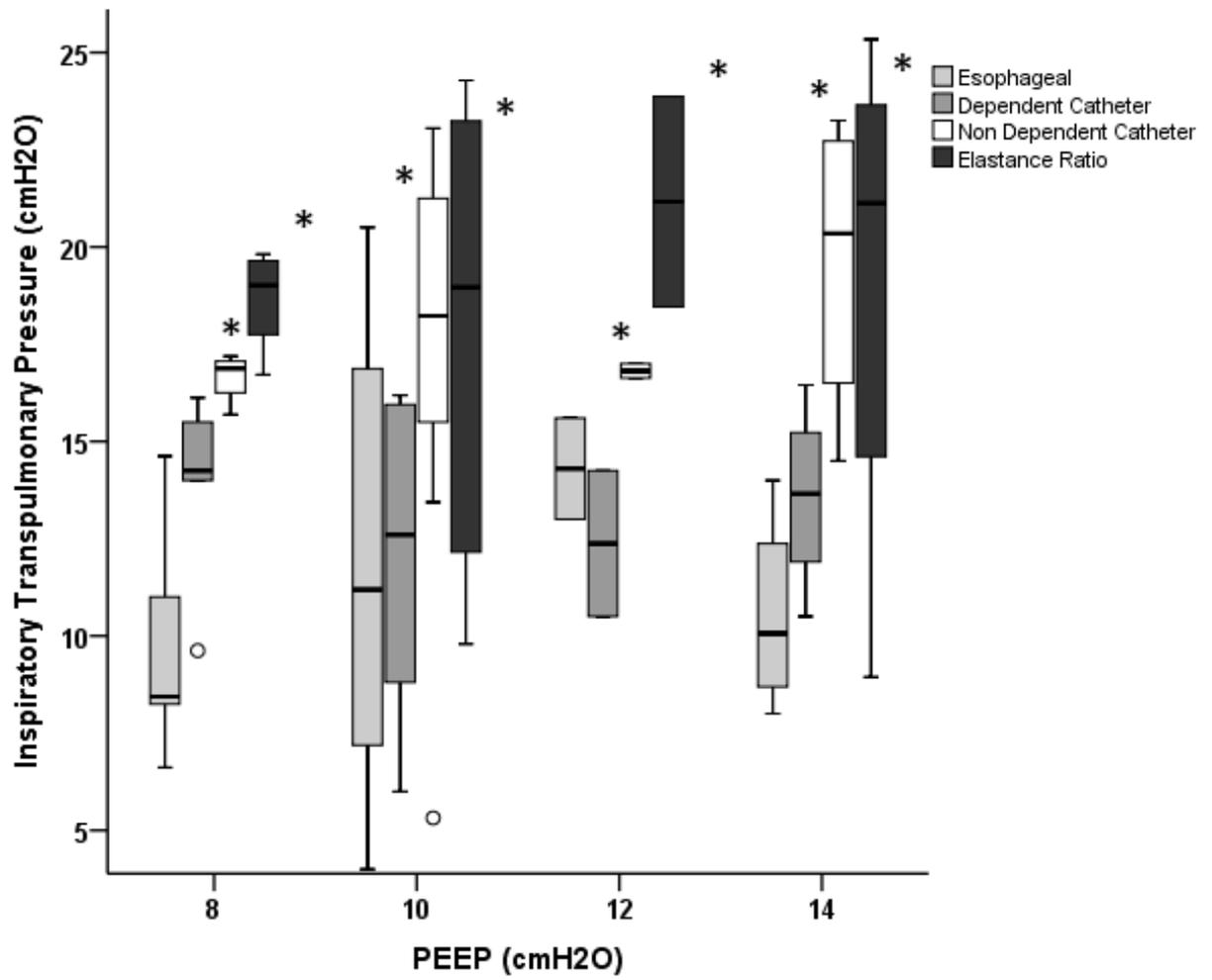
Figure 5

(A)



Figures 5

(B)



Supplementary Figure 1

Picture of positioning of pleural catheters during surgery and corresponding post-operative CT-scan in one patient.

