Feasibility of Lung and Diaphragm-Protective Ventilation: Preliminary Results of the LANDMARK Clinical Trial

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Background: Because of the conflicting benefits and risks of spontaneous breathing, it is uncertain whether safe spontaneous breathing can be achieved in patients with AHRF. Clinical observations suggest that a higher positive end-expiratory pressure (PEEP) ventilation strategy and extracorporeal CO_2 removal ($ECCO_2R$) may help to attenuate potentially injurious respiratory effort. We undertook to assess the feasibility and safety of a novel lung and diaphragm-protective ventilation (LDPV) strategy in patients with AHRF and to determine whether higher PEEP and varying $ECCO_2R$ could facilitate LDPV targets.

Methods: We conducted a randomized cross-over trial of higher vs lower PEEP levels in patients with AHRF defined by a PaO_2/FiO_2 <300 and the need for invasive mechanical ventilation with or without veno-venous extracorporeal membrane oxygenation (VV-ECMO). Low PEEP (defined as lowest tolerated PEEP level with a minimum of 6 cm H_2O while maintaining $FiO_2 \leq 0.8$) and high PEEP (defined as end-expiratory $P_L > 0$ cmH_2O with a minimum of 15 cmH_2O) were applied in random order. At each PEEP level, a standardized algorithm for titrating inspiratory pressure and sedative infusions was applied to determine whether LDPV targets for respiratory effort (quantified by esophageal pressure swing, ΔPes of 3-8 cmH_2O) and transpulmonary driving pressure ($\Delta P_{L,dyn} < 15$ cmH_2O) could be achieved. In patients receiving VV-ECMO, sweep gas flow was lowered to the minimum tolerated level (pH>7.3 and respiratory rate<35) during the PEEP trial; they then underwent a third titration stage where sweep gas flow was increased up

to a maximum of 10 L/min to obtain high $ECCO_2R$. The primary outcome was the proportion of patients in whom the targets were achieved under each condition.

Results: This preliminary analysis includes 21 patients (baseline characteristics are reported in Table 1). Three patients (14%) could not complete both PEEP levels in the trial. Overall, LDPV targets were achieved at either higher or lower PEEP levels in 14/21 patients (67%); 7/9 (78%) patients receiving VV-ECMO achieved the targets; 7/12 (58%) patients not on VV-ECMO achieved the targets (Figure 1). LDPV targets were achieved only at high PEEP in 5/21 (24%) patients; only at lower PEEP in 3/21 (14%), and at both PEEP levels in 5/21 (24%). Among patients on VV-ECMO, 1/7 (14%) could not achieve targets at either higher or lower PEEP at minimum sweep gas flow (mean 3.5, SD 0.9 L/min) but achieved the targets at high sweep gas flow (mean 9.5, SD 0.5 L/min). The association between PEEP level and respiratory effort varied widely among patients: (mean difference in ∆Pes at higher vs. lower PEEP -1.5 cmH2O, SD 4.5); higher PEEP was associated with a decrease in ∆Pes of at least 3 cm H_2O in 9/21 patients (vs. 6/21 patients at lower PEEP); an increase in ΔPes of at least 3 cm H2O was seen in 1/21 patients at higher PEEP vs. 0/21 patients at lower PEEP. Similarly, in patients on VV-ECMO the association between sweep gas flow and respiratory effort varied widely (mean difference in ∆Pes at higher vs. lower sweep gas flow -7 cmH2O, SD 7).

Conclusion: Preliminary results of this trial suggest a LDPV strategy is feasible in many patients with AHRF. Increasing PEEP and sweep gas flow can reduce inspiratory effort in some patients but the effect is variable.

Table 1. Baseline characteristics

	Failure (n=7)	**Success (n=14)**	**Total (n=21)**	**p=**
Age, mean (SD)	40 (10)	51 (17)	51 (15)	0.695
Female sex, n (%)	2 (28%)	6 (42%)	8 (38%)	0.525
PaO$_2$/FiO$_2$ category, n (%) **≥200** **<200** **ECLS**	2 (28.6%) 3 (43%) 2 (28.6%)	4 (28.6%) 3 (21.4%) 7 (50%)	6 (28.6%) 6 (28.6%) 9 (43%)	0.535
Respiratory frequency	28 (9)	26 (10)	27 (10)	0.804
V$_T$, mean (SD)	422 (164)	386 (126)	398 (136)	0.585
PEEP, mean (SD)	10 (4)	11 (4)	11 (4)	0.394
Crs, mean (SD)	24 (14.5)	26 (10)	25.5 (11)	0.799
PaO$_2$/FiO$_2$, mean (SD)	91 (47)	116 (54)	108 (52)	0.345
Propofol (µg/kg/min), mean (SD)	33 (38)	31 (21)	32 (27)	0.643
Fentanyl (µg/kg/min), mean (SD)	75 (92)	97 (106)	90 (99)	0.350

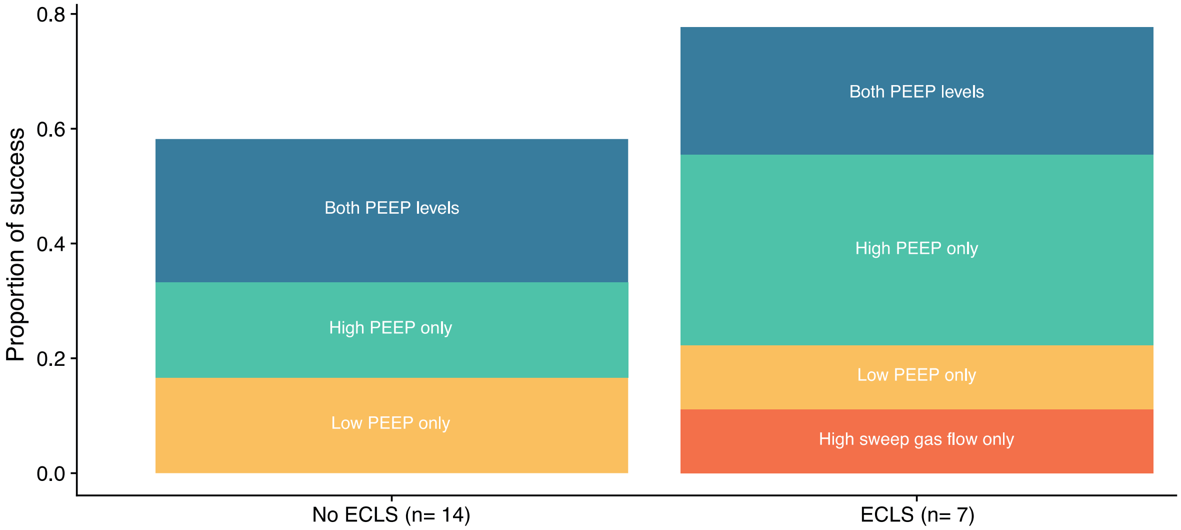

Fig 1. Success rate of the LDPV strategy in patients with and without ECLS.

Proportion of patients in which the LDPV algorithm was successful at either the high PEEP, low PEEP or both PEEP stages in the no ECLS and ECLS groups. 1 of the 7 (14%) patients in the ECLS group succeeded only at the high sweep gas flow strategy stage.

Optimal esophageal pressure catheter balloon filling volume in mechanically ventilated children

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Background Esophageal pressure (Pes) manometry allows assessment of respiratory mechanics, enabling individualized titration of respiratory support. Pes can be measured by specifically designed catheters, equipped with a small inflatable balloon. In adults, it has been recommended to perform an individual calibration procedure by creating a pressure volume loop of the balloon to determine the optimal filling volume.[1] We sought to explore if this would also hold true for pediatric patients.

Objectives To identify optimal balloon filling volume in mechanically ventilated children and its effect on measured transpulmonary pressure

Methods Mechanically ventilated sedated and/or paralyzed pediatric patients (<18years) with an esophageal catheter (6Fr pediatric or 8Fr adult size Vyaire (Yorba Linda, CA (USA))) in situ were included. The esophageal balloon was inflated incrementally by steps of 0.2mL (respectively maximum 1.6mL and 2.6mL). Respiratory holds were performed at the end of each step. Pressure-volume loops were obtained for visual identification of the minimal, maximal and optimal filling volume. The optimal filling volume was defined as the volume where the highest dPes, between inspiratory and expiratory holds, was measured within the range of the minimum and maximum filling volume.

Results Fifty-seven subjects were included, of whom 16 were excluded (due to (suspected) malposition or technical reasons). Of the remaining 41 patients, median age 6.5 months [2, 25], optimal balloon volumes were obtained. In 80% of the cases a 6Fr pediatric catheter was used. The range of the obtained optimal filling volume for the 6 Fr catheter was 0.2mL to 1.2mL, median 0.6mL. For the 8Fr adult catheter (n=8) the optimal filling volume varied from 0.2 to 2.0mL. In the 6Fr catheter, the end-expiratory transpulmonary pressure at 0.6mL compared to individualized Vbest did not differ significantly, nor did it for the end-inspiratory transpulmonary pressure.

Conclusions the optimal filling volume for the esophageal catheter varies in the pediatric patient, albeit that there appeared to be no significant effect on transpulmonary pressure values.

Key words pediatric, mechanical ventilation, transpulmonary pressure, esophageal pressure, personalized medicine

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Evolution of Diaphragm Echodensity and Clinical Outcomes in Mechanically Ventilated Patients

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Rationale: Acute increases in muscle sonographic echodensity reflect muscle injury. Changes in echodensity of the diaphragm during mechanical ventilation and their relationship to clinical outcomes have not been characterized.

Objectives : To characterize changes in diaphragm echodensity during mechanical ventilation and to establish whether these changes are associated with prolonged mechanical ventilation.

Methods: Diaphragm ultrasound images were prospectively collected in mechanically ventilated patients and in 10 healthy controls.

Measurements: Echodensity was quantified by describing the right-skewed distribution of grayscale values (50th percentile, ED50; 85th percentile, ED85). Outcomes ascertained included time to liberation from ventilation and ICU complications (including reintubation, tracheostomy, prolonged ventilation, or death).

Main Results: Echodensity measurements were obtained serially in 34 patients comprising a total of 104 images. Baseline (admission) diaphragm ED85 was higher in mechanically ventilated patients compared to healthy subjects (median 56, interquartile range (IQR) 42–84, vs. 39, IQR 36–52, $p=0.04$). Patients with an initial increase in median echodensity over time ($\geq +10$ in ED50 from baseline) had fewer ventilator-free days to day 60 ($n=13$, median 46, IQR 0–52) compared to patients without this increase ($n=21$, median 53 days, IQR 49–56, unadjusted $p=0.03$). Both decreases and increases in diaphragm thickness during mechanical ventilation were associated with increases in ED50 over time (adjusted $p=0.03$, conditional $R^2=0.80$).

Conclusions: Many patients exhibit increased echodensity at the outset of mechanical ventilation. Increases in diaphragm echodensity are associated with prolonged mechanical ventilation. Both decreases and increases in diaphragm thickness during mechanical ventilation are associated with increased echodensity.

CHANGES IN LUNG PHYSIOLOGY DURING PROGRESSIVE LOWERING OF RESPIRATORY RATE IN HEALTHY PIGS UNDERGOING ECMO

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Background: Ultra-protective mechanical ventilation during Extracorporeal Membrane Oxygenation (ECMO) is aimed at reduction of mechanical power by lowering of tidal volume (Vt) and respiratory rate (RR). Reducing RR may decrease the risk of Ventilatory Induced Lung Injury but it might also induce alveolar de-recruitment. However, dissecting de-recruitment due to lung edema vs. the fraction due to hypo-ventilation may be challenging in injured lungs. We took a step backward to characterize changes in lung physiology associated with progressive RR reduction during ECMO in healthy animal lungs.

Methods: Six female pigs (39.7±4.2 kg) underwent general anesthesia and volume control ventilation (Baseline VCV: PEEP 5 cmH$_2$O, Vt 10 ml/kg, I:E=1:2, FiO$_2$ 0.5, RR 24). After, VV-ECMO cannulation was performed, and RR was reduced to 18, 12 and 6 (fixed order, 6 hours per step), while all other VCV settings remained unchanged. During each RR phase, ECMO blood flow was kept constant at 1.5 l/min while gas flow was increased to maintain PaCO$_2$ within ±5 mmHg from Baseline. At Baseline (without ECMO) and towards the end of each RR-ECMO phase, data from ECMO, gas exchange, quantitative CT scan, ventilation distribution by Electrical Impedance Tomography (EIT) and ventilation pressures were collected.

Results: Increasing ECMO gas flow while lowering RR was associated with an increase in the fraction of non-aerated tissue (Baseline median 2 [IQR 1-5]% vs. RR18 2 [1-4]% vs. RR12 5 [3-9]% vs. RR6 9 [7-16]%, $p=0.002$) and with a decrease of tidal ventilation reaching the gravitationally-dependent lung regions (Baseline 71±5% vs. RR18 71±6% vs. RR12 66±10% vs. RR6 62±11%, $p=0.018$). The fraction of non-aerated lung was correlated with longer expiratory time spent at zero flow ($r=0.555$, $p=0.011$), and not to plateau or mean airway pressure ($r=0.102$, $p=0.636$ and $r=-0.333$, $p=0.111$, respectively).
Intrapulmonary shunt increased at lower RR (Baseline 6±3% vs. RR18 11±1% vs. RR12 10±2% vs. RR6 13±3%, $p<0.001$) and PaO$_2$ decreased (Baseline 263±23 vs. RR18 250±24 vs. RR12 254±18 vs. RR6 218±23 mmHg, $p<0.001$). Increased shunt was associated with lower PaO$_2$ ($r=-0.700$, $p<0.001$). Increasing ECMO gas flow decreased the respiratory exchange ratio (RER) of the natural lung (Baseline 0.74±0.09 vs. RR18 0.87±0.11 vs. RR12 0.78±0.12 vs. RR6 0.46±0.13, $p<0.001$) resulting in lower PAO$_2$ (RR24 312±6 mmHg vs. RR18 321±4 mmHg vs. RR12 315±7 mmHg vs. RR6 300±12 mmHg; $p<0.001$). PaO$_2$ was significantly correlated with PAO$_2$, as well ($r=0.568$, $p=0.005$). Shunt and PaO$_2$ were not correlated with the fraction of non-aerated lung ($r=0.204$, $p=0.350$ and $r=-0.353$ $p=0.091$, respectively).

Conclusions: Progressive decrease of RR coupled with increasing CO$_2$ removal by ECMO in mechanically ventilated healthy pigs leads to development of lung atelectasis, higher shunt and poorer oxygenation. Underlying mechanisms for lung collapse may include longer motionless expiratory time.

Abdominal Muscle Ultrasound and Weaning Outcomes in Mechanically Ventilated Patients

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Introduction: The abdominal muscles play an important role in maintaining ventilation during loaded breathing and are crucial for cough function. Ultrasound measurements of abdominal muscles thickness and thickening fraction (TF) may be useful to assess abdominal muscle structure, activity, and function in mechanically ventilated patients.

Objectives: To establish the feasibility and reproducibility of abdominal muscle thickness and TF measurements in mechanically ventilated patients, to compare these measurements between healthy subjects and mechanically ventilated patients, and to establish the relationship between abdominal muscle TF during tidal breathing or coughing and weaning outcomes.

Methods: In 57 mechanically ventilated patients and 20 healthy subjects, thickness and TF of right external oblique (EO), internal oblique (IO), transversus abdominis (TrA) and rectus abdominis (RA) were measured before and during a spontaneous breathing trial (SBT) and during coughing.

Results: Abdominal muscle thickness and TF measurements were obtained in all patients and reproducibility was acceptable for IO and RA (median TF 11% IQR 6–22 and 7% IQR 4–10, coefficient of reproducibility 11% and 5%, respectively). Compared to healthy subjects end-inspiratory thickness of RA (14 mm IQR 12–16.4 *vs* 6.9 IQR 5.2–8.4), IO (13.5 IQR 10.6–18.5 *vs* 4.4 IQR 3.6–6) and TrA (5.3 IQR 4.2–7.6 *vs* 2.4 IQR 1.9–3.2) was lower in mechanically ventilated patients (p< 0.001 in all cases). TF_{TrA} during coughing was also lower in mechanically ventilated patients (50% IQR 27–80 *vs* 89% IQR 54–109, p= 0.03). Despite a great overlap between groups, at 5 minutes into the SBT the absolute change in TF from baseline (pre-SBT) of TrA and IO increased substantially in patients failing the SBT compared to patients who passed the SBT (difference 13.2%, 95%CI 0.9–24.8 and 7.2%, 95%CI 2.2–13.2, respectively) (Figure 1).
Based on the observed pattern of abdominal muscle thickening during coughing in healthy subjects, we defined a global measure of abdominal muscle function based on the sum of TF_{RA}, TF_{TrA} and TF_{IO} during coughing ($coughTF_{abs}$).
Among patients extubated (n= 32), reduced $coughTF_{abs}$ was associated with an increased risk of extubation failure (OR 2.1, 95%CI 1.1-4.4 per 10% decrease in thickening fraction) and exhibited moderately high predictive discrimination (AUROC= 82%, 95% CI 59–100%) (Figure 2). Of

patients with reduced coughTF_{abs} < 90% (lower limit of normality in healthy subjects), 50% required reintubation.

Conclusions: Abdominal muscle structure, activity and function can be reliably assessed by ultrasound in mechanically ventilated patients. The thickness of RA, IO, and TrA was substantially lower in mechanically ventilated patients compared to healthy subjects. IO and TrA TF was higher in patients failing an SBT compared to patients who passed, consistent with elevated expiratory muscle effort. In patients who passed an SBT, reduced abdominal muscle thickening during coughing was associated with a high risk of extubation failure.

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Figure 1.

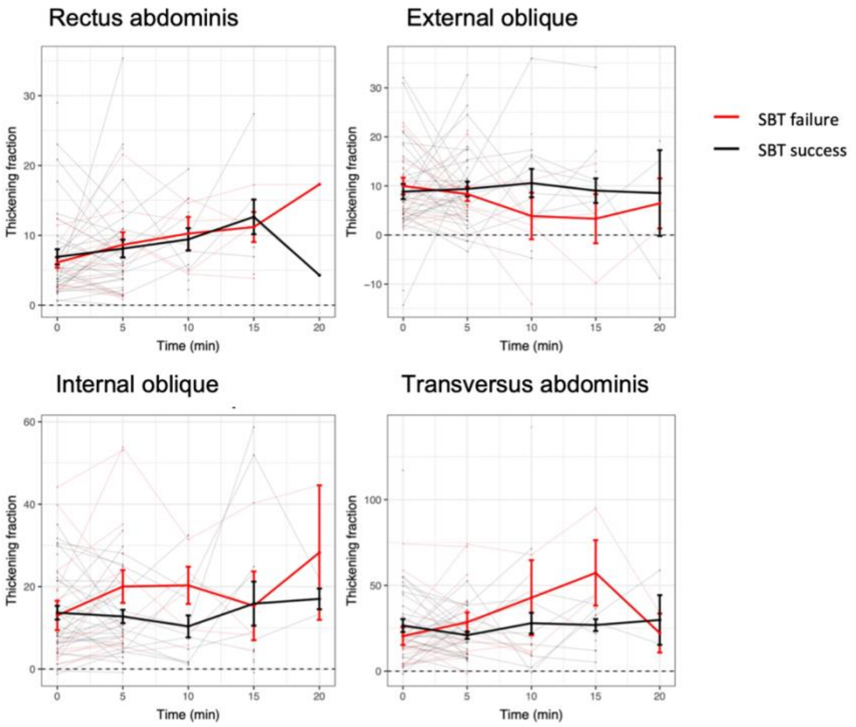
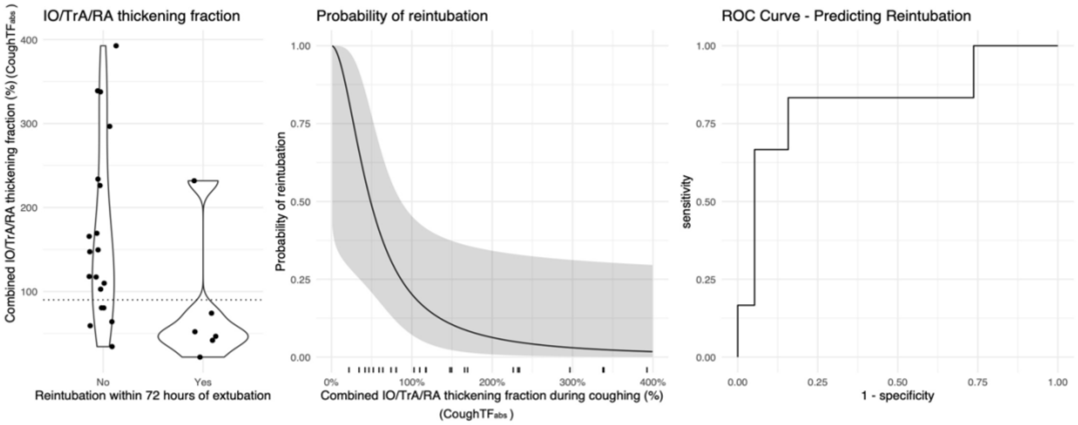


Figure 2.



POSITIVE END-EXPIRATORY PRESSURE AND PLEURAL PRESSURE DURING PRONATION: AN EXPERIMENTAL STUDY

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*Co-First Authors, #BPK died June15, 2019, the study is dedicated to his memory.

Introduction: Prone position improves oxygenation and mortality in ARDS. The physiological basis of lung protection and the impact of PEEP during pronation in ARDS are not fully elucidated. We hypothesized that pronation improves homogeneity of ventilation and stress by reducing the vertical gradient of pleural pressure.

Objectives: To compare pleural pressure (Ppl) gradient, ventilation distribution and regional compliance between dependent and non-dependent lung, and investigate the effect of PEEP during supination and pronation

Methods: We used a 2-hit model of lung injury (saline lavage and high-volume ventilation) in 14 mechanically ventilated pigs and studied supine and prone position. Global and regional lung mechanics including dependent and non-dependent Ppl and distribution of ventilation (Electrical Impedance Tomography) were analyzed across PEEP steps from 20 to 3 cm H2O. Two pigs underwent CT scan: tidal recruitment and hyperinflation were calculated. Distribution of ventilation was studied in human cadavers.

Results: Pronation improved oxygenation (at low PEEP - 167 ± 57 vs 70 ± 5), increased regional Ppl (at PEEP 5 cmH_2O, Supine vs Prone ND Ppl 1.5 ± 1.4 vs 3.9 ± 2.2, Supine vs Prone D Ppl 7.9 ± 1.1 vs 8.1 ± 2.2), thus decreasing transpulmonary pressure for any PEEP, and reduced the dorso-ventral Ppl gradient at PEEP < 10cmH_2O. Distribution of ventilation was homogenized between dependent and non-dependent while prone and was less dependent on the PEEP level than supine. The highest regional compliance was achieved at different PEEP levels in dependent and non-dependent regions in supine (15 and 8 cmH_2O), but for similar values in prone (13 and 12 cmH_2O). Tidal recruitment was more evenly distributed (dependent/non-dependent); hyperinflation lower and lungs cephalocaudally longer in the prone position. Regional homogenization was also observed in a human cadaver.

Conclusions: In this lung injury model, pronation reduces the vertical pleural pressure gradient and homogenizes regional ventilation and compliance between the dependent and non-dependent regions. Homogenization is much less dependent on PEEP level than in supine. Setting PEEP is much safer during pronation compared to supination.

PEEP titration using different electrical impedance tomography based strategies in patients with acute respiratory distress syndrome: a physiological study.

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Introduction: Electrical impedance tomography (EIT) is a promising technique allowing to assess regional lung ventilation. Different strategies using EIT have been proposed to individualize positive end expiratory pressure (PEEP) titration in patients with acute respiratory distress syndrome (ARDS). The aim of this study was to compare the optimal PEEP levels determined by these different EIT based strategies and by a respiratory mechanics-based strategy (Express strategy).

Methods: A decremental PEEP trial from PEEP 20 to 5 cmH_2O was performed in 19 patients with ARDS (Step of 3 cmH_2O during 3 minutes). For each patient, the optimal PEEP level was determined using 4 EIT-based different strategies : (1) PEEP level associated with the lowest "global inhomogeneity index" (GI) ; (2) PEEP level associated with the "center of ventilation" (CoV) closest to 0.5 ; (3) PEEP level corresponding to the intersection of the "overdistension" (OD) and "lung collapsus" (LC) curves as proposed by Costa et al. ; (4) PEEP level corresponding to the minimal OD with a LC < 15% in the Costa's method. These PEEP levels were also compared to the PEEP level set to reach a plateau pressure of 28 to 30 cmH_2O, as described in the ExPress study. In addition, three reconstructions of OD and LC curves were performed using 3 acquisition windows for decremental PEEP trial: (1) from 20 to 5, (2) 17 to 5 and (3) 20 to 8 cmH_2O. Respiratory mechanics and PaO_2/FiO_2 ratio were assessed at PEEP 5 and 15 cmH_2O.

Results: There was no significant difference in optimal PEEP levels determined by the ExPress, GI and CoV methods (17 [15.5 – 17] ; 17 [14 – 20] and 20 [17 – 20] cmH_2O, respectively). Optimal PEEP based on the Costa's algorithm was significantly lower with the intersection method (9.5 [8 - 10.75] ; $p < 0.001$) and the minimal OD with LC < 15% (11.0 [8 - 12.5], than in the 3 others strategies ($p < 0.001$). In the 2 methods using Costa's algorithm, significantly higher PEEP levels were obtained with a 20-8 cmH_2O PEEP acquisition window than with a 17-5 cmH_2O range. The PEEP level determined by the different strategies was not correlated with respiratory system compliance and oxygenation at PEEP 5 cmH_2O, and with response in oxygenation after PEEP increase.

Conclusion: EIT-based and respiratory mechanics based strategies for PEEP titration lead to significantly different optimal PEEP values. The use of different PEEP ranges during decremental PEEP trial can induce variations in the optimal PEEP computed by the Costa's algorithm.

Role of PEEP and Regional Transpulmonary Pressure in Asymmetrical Lung Injury.

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Rationale: Asymmetrical lung injury is a frequent clinical presentation and the effects of PEEP remain unclear. It is widely believed that increasing PEEP to recruit the non-injured lung result in risk of hyperinflation of the less-injured lung. Hence the current suggested setting in this scenario is a low PEEP approach. The validity of esophageal pressure (P_{es}) in this context is also unknown.

Objectives: To compare P_{es} with directly measured pleural pressure (P_{pl}) and investigate how PEEP impacts on ventilation distribution and regional driving transpulmonary pressure (DP_L) during asymmetrical lung injury.

Methods: In 14 mechanically ventilated pigs, lung injury was induced selectively in one of the two lungs. To achieve asymmetrical injury, one lung was blocked while the contralateral one underwent surfactant lavage followed by injurious ventilation. Airway pressure (P_{aw}), dorsal and ventral P_{pl} in the two lungs and P_{es} were measured. Distribution of ventilation was assessed by Electrical Impedance Tomography (EIT). A decremental PEEP trial from PEEP 20 to 0 cmH_2O was perform after a recruitment manoeuvre in normal lungs first and after asymmetrical injury secondly. Pressure-volume curve (P-V curve) of single lung and whole lung were obtained before and after injury.

Results: Asymmetrical lung injury was obtained. Surprisingly ventral P_{pl} and dorsal P_{pl} remained similar in the injured and the non-injured lung across PEEP levels, equalizing inside the respiratory system. P_{es} reflects the dorsal P_{pl} of both sides very similarly compared to ARDS model (Figure 1). V_T distribution between the two lungs was homogenized by increasing PEEP (Figure 2) but with significant hyperinflation associated (Figure 3). The regional changes in DP_L were similar in the two lungs across PEEP levels and reflect mainly regional V_T redistribution (Figure 4).

Conclusions: Despite asymmetrical lung injury, P_{pl} between injured and non-injured lungs is equalized and esophageal pressure is a reliable estimate of dorsal P_{pl}. Driving transpulmonary pressure is similar for both lungs and V_T distribution results from regional C_{rs}. Moderate PEEP is beneficial for both lungs.

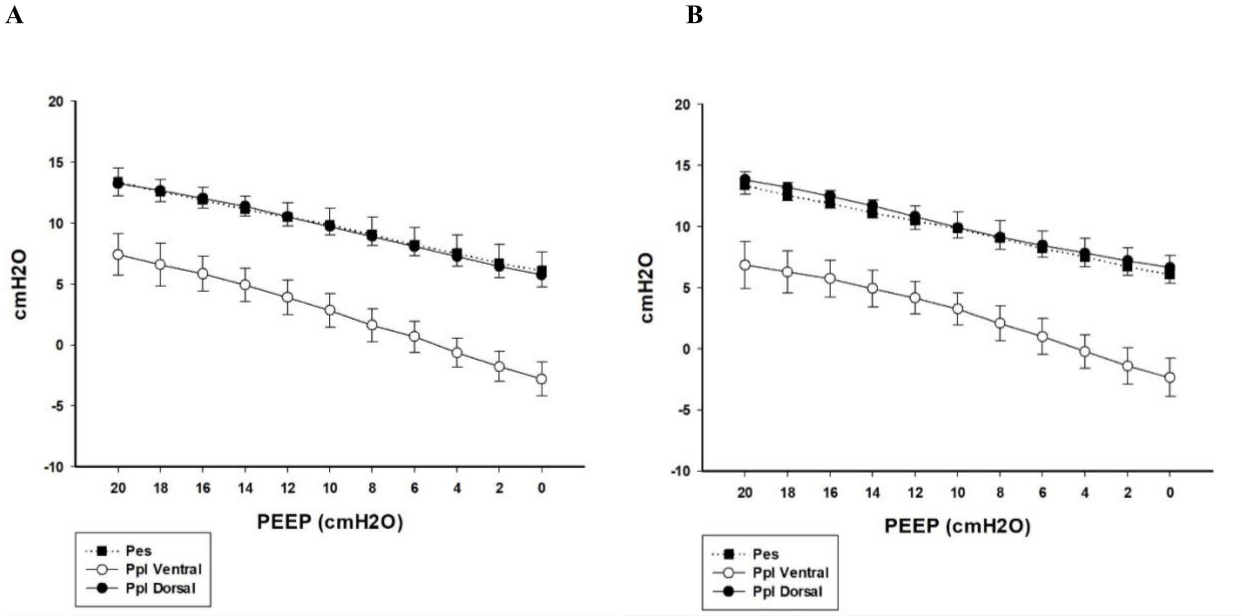

Figure 1. Relationship between P_{pl} recorded ventrally and dorsally in the left and right lung and P_{es} at End-Expiration across PEEP. A) Non-injured Lung. B) Injured Lung. The dorsal P_{pl} is overlapping the P_{es} value across all PEEP levels. Between Injured and Non-Injured Lung minimal change is occurring in both ventral and dorsal Ppl.

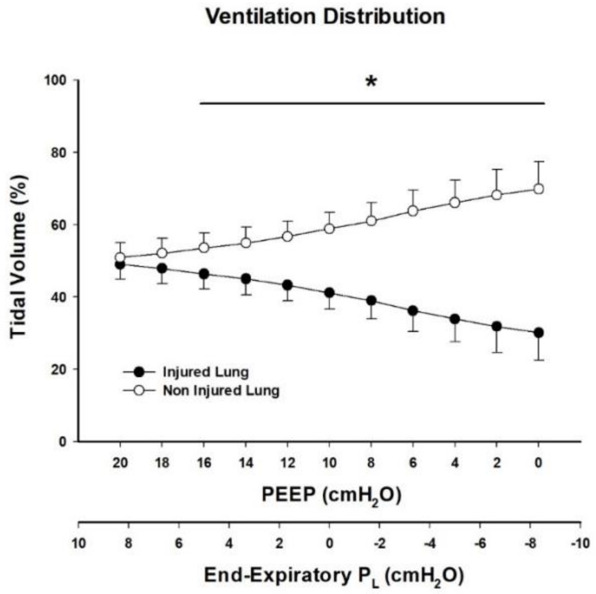

Figure 2. Tidal Volume (V_T) distribution express as a percentage of total V_T in the injured and non-injured lung across PEEP. V_T distribution has been recorded with EIT device. High PEEP homogenizes the system with an even distribution of V_T. * $P<0.05$.

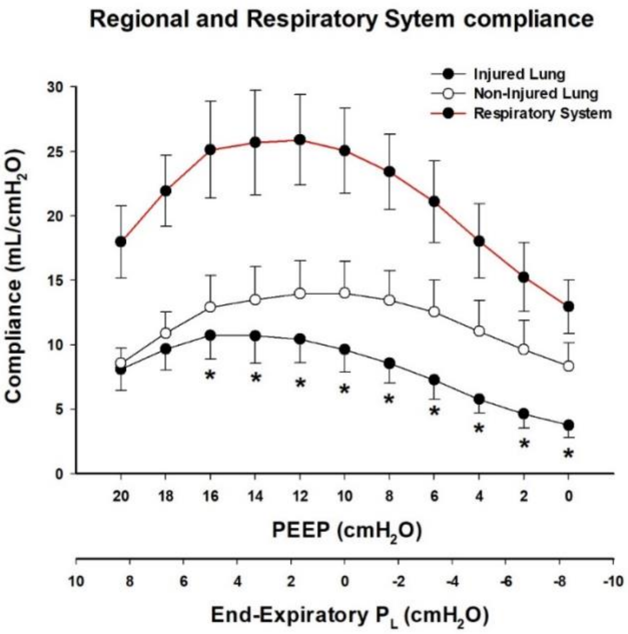

Figure 3. Single lung and both lungs respiratory system compliance (C_{rs}). The red line reflects both lungs C_{rs} (calculated as tidal volume/driving pressure), with the best C_{rs} at PEEP 12 cmH$_2$O. The two black lines reflect single lung C_{rs} (white dots = non- injured lung, black dots = injured lung; calculated as regional tidal volume derived from EIT/driving pressure), the two regional C_{rs} are statistically different form ZEEP to PEEP 16 cmH$_2$O. Best non-injured lung C_{rs} at PEEP 10 cmH$_2$O, best injured lung C_{rs} at PEEP 14 cmH$_2$O.

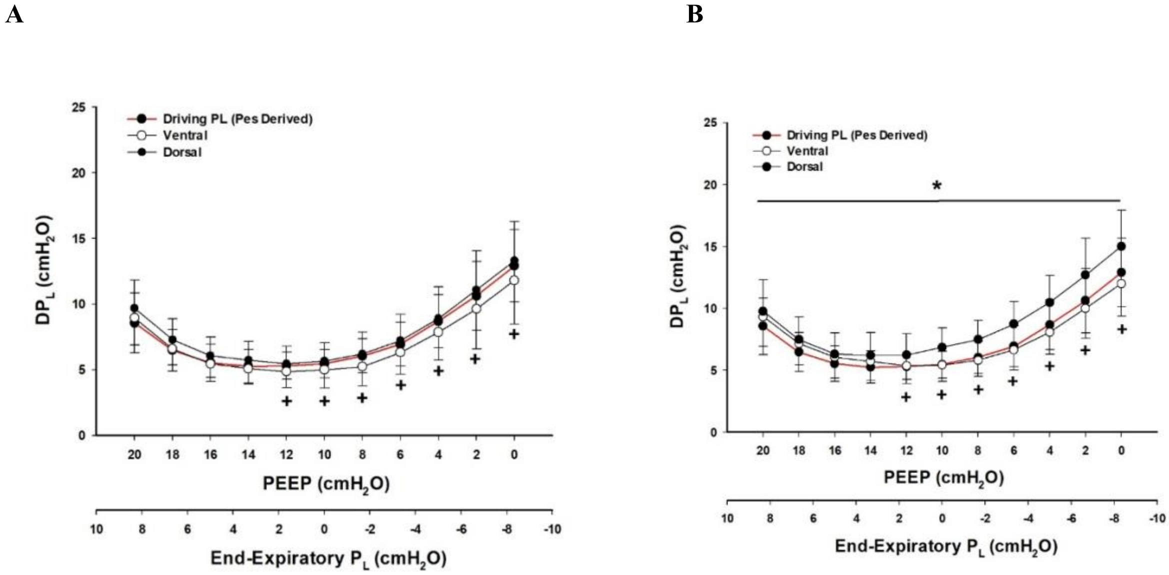

Figure 4. Relationship between Regional Driving Transpulmonary Pressure (Regional DP$_L$) calculated using Ppl catheters and Driving Transpulmonary Pressure (DP$_L$) calculated using Pes. A) Non-Injured Lung. B) Injured Lung. DP$_L$ is a good estimation of any Regional DP$_L$. The regional DP$_L$ absolute values between Injured Lung and Non Injured Lung are similar suggesting similar tidal stress in the two lungs. * $P<0.05$ Dorsal DP$_L$ compared to DP$_L$ from P_{es}. + $P<0.05$ Dorsal DP$_L$ compared to Ventral DP$_L$.

Effect of a conservative approach to the start of mechanical ventilation on ventilator-free days in coronavirus disease 2019 (COVID-19) pneumonia after adjustment by inverse probability of treatment weighting.

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Introduction: High flow nasal cannula (HFNC) decreases the need for intubation in patients with acute respiratory failure (ARF). However, delaying intubation has been linked to worse patients' outcome in the acute respiratory distress syndrome (ARDS).

Methods: Prospectively once-daily collected database including patients admitted to 36 Spanish ICUs. On August 13th, we identified 686 patients that had received either HFNC (183) or intubation (503) on ICU admission day. Ventilator-free days (VFD) at 28 days and in-hospital mortality were compared between groups after adjustment with inverse probability of treatment weighting. Deceased individuals were assigned 0 VFDs. Since 6% of the data was missing, multiple imputation with a Markov chain Monte Carlo method was carried out prior to estimate the probability of receiving intubation using a logistic regression model with variables selected based on both subject matter knowledge and showing univariate association with VFD. The final model included age, gender, systolic blood pressure, pH, respiratory rate, SOFA, Glasgow Coma Scale, platelet, leucocyte and lymphocyte count, lactate, D-dimer and hospital (categorized in four quartiles). Goodness of fit was assessed comparing standardized mean differences in the adjusted population.

Results: Patients treated with HFNC had 6 VFDs more (95% CI 2-11, $p<0.001$) while mortality was similar [absolute difference -4%, -22%-14%, $p=0.21$].

Conclusions: HFNC could decrease the need for intubation without affecting mortality in severe COVID-19 pneumonia.

Effect of Early Mobilization from Bed to Wheel Chair on Regional Ventilation Distribution Assessed by Electrical Impedance Tomography in Respiratory Failure Patients

Siyi Yuan， Huaiwu He， Yun Long， et al.

Backgrounds: There was limited knowledge about the effect of early mobilization on regional lung ventilation in patients with respiratory failure. The aim of the study was to examine whether electrical impedance tomography (EIT) could help to predict the improvement in ventilation distribution due to mobilization.

Methods: Forty-one patients with respiratory failure, who had weaned from ventilator and received early mobilization were prospectively enrolled in this study. EIT was used to assess regional lung ventilation distributions at 4 timepoints during the early mobilization from bed to wheelchair (T_{base}: baseline, supine position at the bed, T_{30min}: sitting position on the wheelchair after 30min, T_{60min}: sitting position on the wheelchair after 60min, T_{return}: return to supine position on the bed after early mobilization). The EIT- based global inhomogeneity (GI) and center of ventilation (CoV) indices were calculated. EIT images were equally divided into four ventral-to-dorsal horizontal regions of interest (ROIs 1-4). Depending on the improvement of ventilation distribution in dependent regions at T_{60min} (threshold set to 15%), patients were divided into recruited (DR) and non-recruited (Non-DR) groups.

Results: From the bed to the wheelchair, a significant and continuous increase of dependent regional ventilation distribution (ROI 3+4: baseline vs. T_{30min}, vs. T_{60min}: 45.9±12.1 vs. 48.7±11.6 vs. 49.9±12.6, p=0.015) and COV (COV baseline vs. T_{30min}, vs. T_{60min}: 48.2±10.1 vs. 50.1±9.2 vs. 50.5±9.6, p=0.003). Besides, there was a significant decrease of GI at T_{60min}. Patients in the DR group (n=18) had significantly higher oxygenation than the Non-DR group (n=23) after early mobilization. $ROI4_{Tbase}$ was significantly negatively correlated to ΔSpO_2 (R=0.72, p□0.001). Using a cut-off value of 6.5%, $ROI4_{Tbase}$had a 79.2% specificity and 58.8% sensitivity to predict response of dependent region recruitment due to early mobilization. The corresponding area under curve was 0.806 (95%CI, 0.677-0.936).

Conclusions: EIT may be a promising tool to predict the ventilation improvement resulted from early mobilization.

Loading of right ventricular ejection by lung inflation during passive mechanical ventilation

Douglas Slobod, Nawaporn Assanangkornchai, Manal Alhazza, Sheldon Magder

Abstract

Rationale: West zone 1 and 2 (non-zone 3) conditions raise the downstream pressure opposing right ventricular (RV) ejection, thereby increasing RV afterload. Previous research demonstrated a discrepancy between the inspiratory rise in the pulmonary artery occlusion pressure (P_{pao}) and the change in esophageal pressure during passive mechanical inspiration, suggesting a non-zone 3 condition. The prevalence of non-zone 3 conditions among mechanically ventilated patients is unknown.

Objectives: Examine the prevalence of non-zone 3 conditions during inspiration across a range of tidal volume (V_T) in passively ventilated patients.

Methods: Prospective, observational study of 34 post-operative cardiac surgery patients with pulmonary artery and esophageal catheters in place. Measurements of plateau pressure, pulmonary artery occlusion pressure (P_{pao}) and the change in esophageal pressure were measured during passive ventilation with a V_T of 2, 4, 6, 8, 10 and 12 ml/kg predicted body weight. Two clinical definitions of non-zone 3 conditions were used. Definition 1 defines a non-zone 3 condition as a change in P_{pao} that exceeds the change in esophageal pressure during passive inspiration. Definition 2 defines a non-zone 3 condition when the plateau pressure exceeds the expected end-inspiratory P_{pao} estimated as the end-expiratory P_{pao} plus the change in esophageal pressure during passive inspiration.

Measurements and Main Results: Non-zone 3 conditions were common during inspiration in this population and their occurrence was associated with higher V_T and driving pressure. According to both definitions, over 60% of patients developed non-zone 3 conditions at a V_T greater than 6 ml/kg predicted body weight, corresponding to a driving pressure of greater than 12 cmH_20. Non-zone 3 conditions were associated with lower end-expiratory P_{pao} and lower lung compliance.

Conclusion: Non-zone 3 conditions are prevalent during the inspiratory phase of passive mechanical ventilation. The hemodynamic consequences of non-zone 3 conditions may explain some of the adverse outcomes associated with ventilating patients at higher V_T and driving pressure.

Effect of Esophageal Pressure-Guided PEEP on Survival from ARDS Depends on Baseline Severity of Multiorgan Dysfunction

Presenter: Jeremy R. Beitler, MD, MPH

Importance: In patients with acute respiratory distress syndrome (ARDS), risk of death is determined by lung injury (disease-attributable risk) and severity of multiorgan dysfunction, among other factors. Patients with less severe multiorgan dysfunction may have relatively higher disease-attributable risk and be likelier to benefit from lung-protective interventions.

Objective: To evaluate whether the effect of esophageal pressure (P_{ES})-guided positive end-expiratory pressure (PEEP) depends on baseline attributable risk of death.

Design: Reanalysis of the EPVent-2 randomized trial.

Setting: 14 North American hospitals.

Participants: Two hundred patients with moderate-to-severe ARDS (PaO_2:$FiO_2 \leq 200$ mm Hg) were enrolled between 2012-2017. Follow-up completed in 2018.

Intervention: Patients were randomly assigned to P_{ES}-guided PEEP or empirical high PEEP. All participants received low tidal volumes.

Main Outcomes and Measures: The main analysis evaluated for heterogeneity of treatment effect on 60-day mortality by severity of multiorgan dysfunction, determined via Acute Physiology and Chronic Health Evaluation-II (APACHE-II). Secondary endpoints included ventilator- and shock-free days. Analyses explored mechanistic plausibility of treatment benefit and harm in subgroups identified by the heterogeneity analysis.

Results: Baseline risk of death from multiorgan dysfunction, predicted by APACHE-II, ranged between 17.7-62.2% (median 37.6%) and was evenly distributed between treatment groups. Treatment effect on 60-day mortality depended on severity of multiorgan dysfunction ($p = 0.03$ for interaction). P_{ES}-guided PEEP significantly lowered mortality among patients with less severe multiorgan dysfunction (HR 0.43, 95% CI 0.20-0.92; $p = 0.03$ for APACHE-II less than median). P_{ES}-guided PEEP was not significantly associated with mortality among patients with more severe multiorgan dysfunction (HR 1.69; 95% CI 0.93-3.05; $p = 0.08$). Effect heterogeneity also was observed for ventilator-free days and shock-free days, with P_{ES}-guided PEEP affording benefit with less multiorgan dysfunction and potential harm with more multiorgan dysfunction. Mechanistic analyses suggested treatment benefit was greatest with PEEP titrated to end-expiratory transpulmonary pressure near 0 cm H_2O.

Conclusions and Relevance: Effect of PEEP strategy on mortality depends on baseline attributable risk. P_{ES}-guided PEEP reduced mortality in patients with less multiorgan dysfunction at baseline, in whom there is a higher attributable risk of death from lung injury.

Feasibility of lung and diaphragm-protective ventilation with and without extracorporeal CO_2 removal in acute respiratory failure: an *in silico* clinical trial

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Introduction: Mechanical ventilation (MV) induces both lung and diaphragm injury. We propose a lung and diaphragm protective ventilation (LDPV) strategy targeting a dynamic transpulmonary pressure (ΔP_L) <15cmH_2O, an esophageal pressure swing (ΔPes) of -3 to -8 cmH_2O, and a pH>7.25. Meeting these targets at the bedside may be complex. We implemented a recently developed physiologically based mathematical model to simulate how patients respond to changes in ventilation, sedation, and extracorporeal CO_2 removal ($ECCO_2R$) to determine which patients could theoretically reach the goals of the LDPV strategy.

Objectives: To estimate the proportion of patients in whom the LDPV target values can be achieved, to determine whether the application of $ECCO_2R$ substantially increases the probability of reaching the targets, and to identify which patients may require $ECCO_2R$ to achieve the LDPV goals.

Methods: We simulated a population of 100 patients with randomly selected baseline physiological characteristics. The main inputs to the model were PaO_2, lung (C_L) and chest wall (C_{CW}) compliance, airway resistance, intrinsic PEEP, V_{CO2}, alveolar dead space fraction (V_{Dalv}/V_T), respiratory rate, and the strong ion difference (SID). These patients were submitted to titration of ventilation and sedation to achieve targets according to a pre-defined algorithm. Patients who were unable to meet the LDPV targets were submitted to gradually increasing levels of $ECCO_2R$ and then the algorithm was re-run. The characteristics of the patients succeeding LDPV with or without $ECCO_2R$ were analyzed in a univariate analysis. Paired sampled t-tests and Wilcoxon rank sum test were performed to determine the effect of variables on the algorithm performance and on the algorithm performance after the use of $ECCO_2R$, respectively. p-value <0.05 are significant.

Results: Of 100 simulated patients (Table 1), 49 patients reached the targets of LDPV without requiring $ECCO_2R$ (15 at baseline, 34 after applying the algorithm). In the 51 patients who failed, none could reach the ΔP_L target and 23/51 could not reach the ΔPes target. LDPV failure was associated with higher alveolar dead space (0.41 vs 0.27, p<0.001), lower lung compliance (44 vs 53 ml/cmH_2O, p=0.0013) and greater metabolic acidosis (strong ion difference 34 vs 37 mEq/l, p<0.049). Of the patients who failed, the application of $ECCO_2R$ enabled 40/51 patients to meet the targets at a median CO_2 removal rate of 30% of V_{CO2} (IQR 17.5-50) from baseline. Eleven patients could not reach LDPV targets even with $ECCO_2R$. The main determinants of failure after $ECCO_2R$ were higher V_{Dalv}/V_T (0.59 vs 0.37, p<0.0001) and lower C_L (34 vs 45 ml/cmH_2O, p=0.011) (Figure 1).

Conclusion: In this *in silico* clinical trial, LDPV targets could be achieved in 49% of our simulated population. $ECCO_2R$ increased the probability of reaching the targets of LDPV from 49% to 89%. The main determinants of failure of LDPV strategy are decreased lung compliance and an increased alveolar dead space to tidal volume ratio.

Usefulness of Airway Occlusion Pressure for to monitor effort and respiratory work during Pressures Support Ventilation.

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Objective. To compare the effort and work of breathing with a new method using data obtained from occlusion pressure maneouver, versus the values obtained by measurements with standard technique by esophageal pressure.

Methods. 33 from 90 cases were included for the study, which showed a good esophageal signal-to-noise ratio and no significant active expiration. Esophageal pressure (Pes), gastric (Pgas), airway pressure (Paw), and airway flow ($\dot{V}$) were registered at 560 Hz for posterior analysis. From each of the 33 recordings, 15 cycles were chosen that included a Baydur test. The Pes was corrected after a linear regression with Paw occluded. The calibration factor for the slope between Pes and Paw was 0.8 to 1.2. The Elastance of the thoracic wall (Etw) was determined during relaxed ventilation.
Respiratory effort (PTP, cmH_2O/sec*min, machine and patient) and work of breathing patient (WOB, j/L) were determined by esophageal-muscle pressure (P musc Eso), and distending pressure from esophageal signal (P Dist Eso) = -P musc Eso + Paw.
We calculated a new parameter, total distending pressure (∫PDist_Occ) as the integral during the inspiration of Paw (∫Paw) plus the product of the half of the delta of occlusion by inspiratory time, in average of 5 cycles prior to occlusion.
The time constant (τ) was calculated from the linear regression between flow and volume in the half middle expiratory of each cycle, the PEEPt was obtained from the Paw trace in the occlusion, the Elastance of the respiratory system (Ers), from the equation $\sum_i^e Ers * V + Ers * \tau * \dot{V}^{\cdot} + PEEPt = \int PDist\_Occ$ by numerical iteration, and the resistances of the respiratory system (Rrs) by multiplying τ * Ers. Ers and Rrs were averaged out of the 5 cycles. A new signal was generated as the occlusion distending pressure (PDist_Occ) in the inspiratory phase of each cycle according to the equation: $PDist\_Occ = E_{rs} * V + R_{rs} * \dot{V} + \dot{P}EEPt$. With PDist_Occ values of PTP (machine and patient) and WOB (patient) were obtained and were compared in each of the 394 cycles with the measurements obtained by standard technique.
Data were expressed as mean ± SD, the comparison was made with Student's t-test and agreement with linear regression and the Bland-Altman analysis.

Results:

WOB (P Dist Eso): 1.21±0.025, WOB (P Dist Occ): 1.19 ±0,026. t = 0.372 p=0.710PTP (P Dist Eso): 545.44± 10.01, PTP (P Dist Occ): 542.74±10.31. t=0.188 p=0.851 (Figures 1,2).

Figure 1. A In red area: P Dist Occ. In purple P Dist Eso.

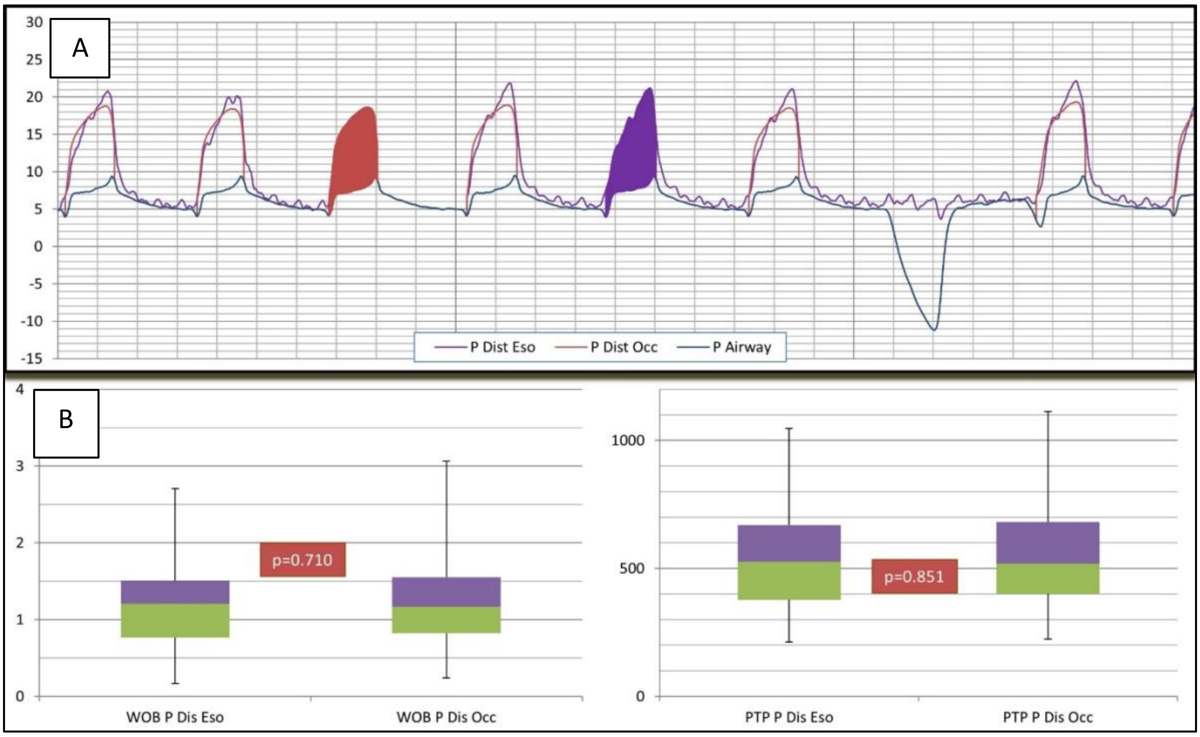
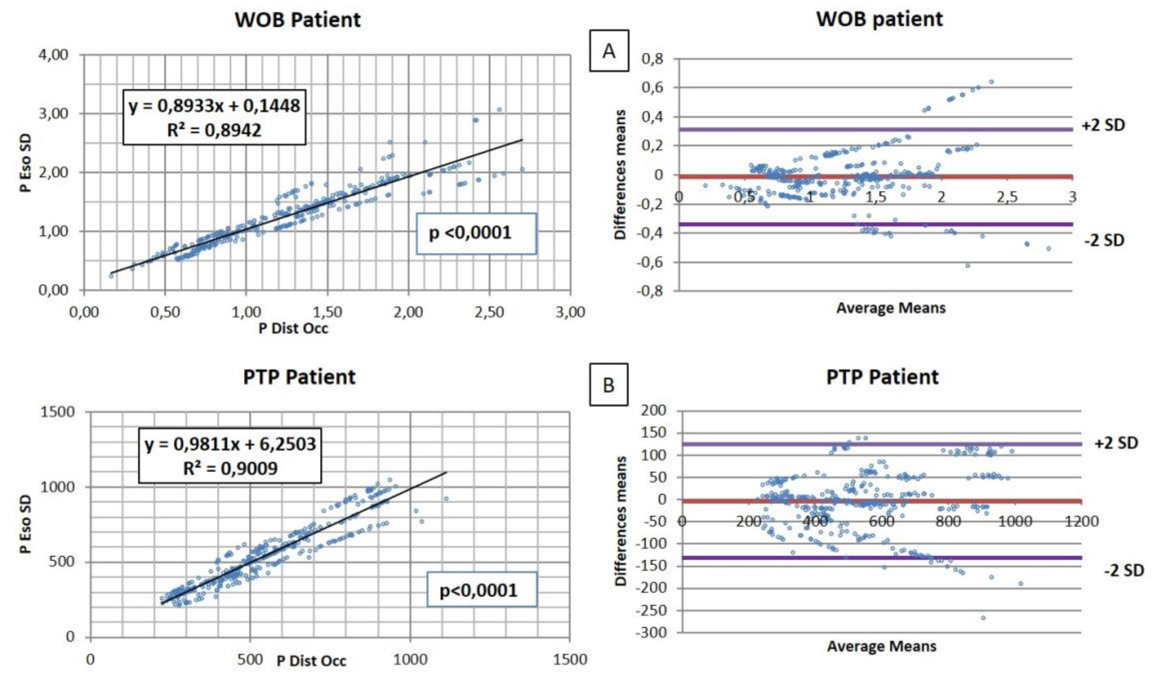


Figure 2



Conclusion: The new method can be used to monitor the patient's respiratory work without the need of the esophageal catheter.

References:

Bertoni M, Telias I, Urner M, et al. A novel non-invasive method to detect excessively high respiratory effort and dynamic transpulmonary driving pressure during mechanical ventilation. Crit Care. 2019;23(1):346.

Monitoring respiratory drive during mechanical ventilation from tracheal pressure.

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Objectives

To assess the usefulness of tracheal pressure (Ptrach) for continuous respiratory drive monitoring.

Methods

We studied 18 patients mechanically ventilated during pressure support ventilation, at maximum sensitivity of the inspiratory trigger and with different levels assistance 7.72±2.90 over PEEP 6.42±1.89cmH_2O

Esophageal (Pes), airways pressure (Paw), Ptrach and flow were registered at 560 Hz.

P100 was measured in Paw between 0 and 300ms after occlusion. The steepest slope in that section was selected (dotted line in red in the figure 1). Ten cycles prior to occlusion were analyzed to measure the Ptrach 100, from nadir backwards and regression every 50 ms. Here too, the steepest slope was selected, dotted line in green.

A total of 151 cycles were analyzed in 18 expiratory occlusion maneuvers.

The results are expressed as mean±SD, median (IRQ), or percentage. The comparisons by t-student. A Bland-Altman and linear regression analyses were performed.

Results

Table 1. Agreement of the measurements of P100 between the both methods.

P100 ms, cmH_2O		**Means (SD)**	**P**	**Means Difference (SD)**	**Limits agreement, CI 95%**	**R^2**
All Data	Tracheal Pressurre	2.74 (1.89) 2.89 (1.88)	0.486	-0.15 (0.41)	-0.98 to 0.67	0.95
	Occlusion Pressure					
Relate to airway occlusion pressure > median (1.72 cmH_2O)	Tracheal Pressurre	4.50 (1.17) 4.58 (1.32)	0.695	-0.08 (0.58)	-1.23 to 1.07	0.81
	Occlusion Pressure					
Relate to airway occlusion pressure < median (1.72 cmH_2O)	Tracheal Pressurre	1.08 (0.25) 1.28 (0.24)	<0.001*	-0.195 (0.20)	-0.6 to 0.21	0.44
	Occlusion Pressure					

Conclusions

Tracheal pressure may be useful for continuous monitoring of respiratory drive. The good fit agrees as the respiratory drive increases.

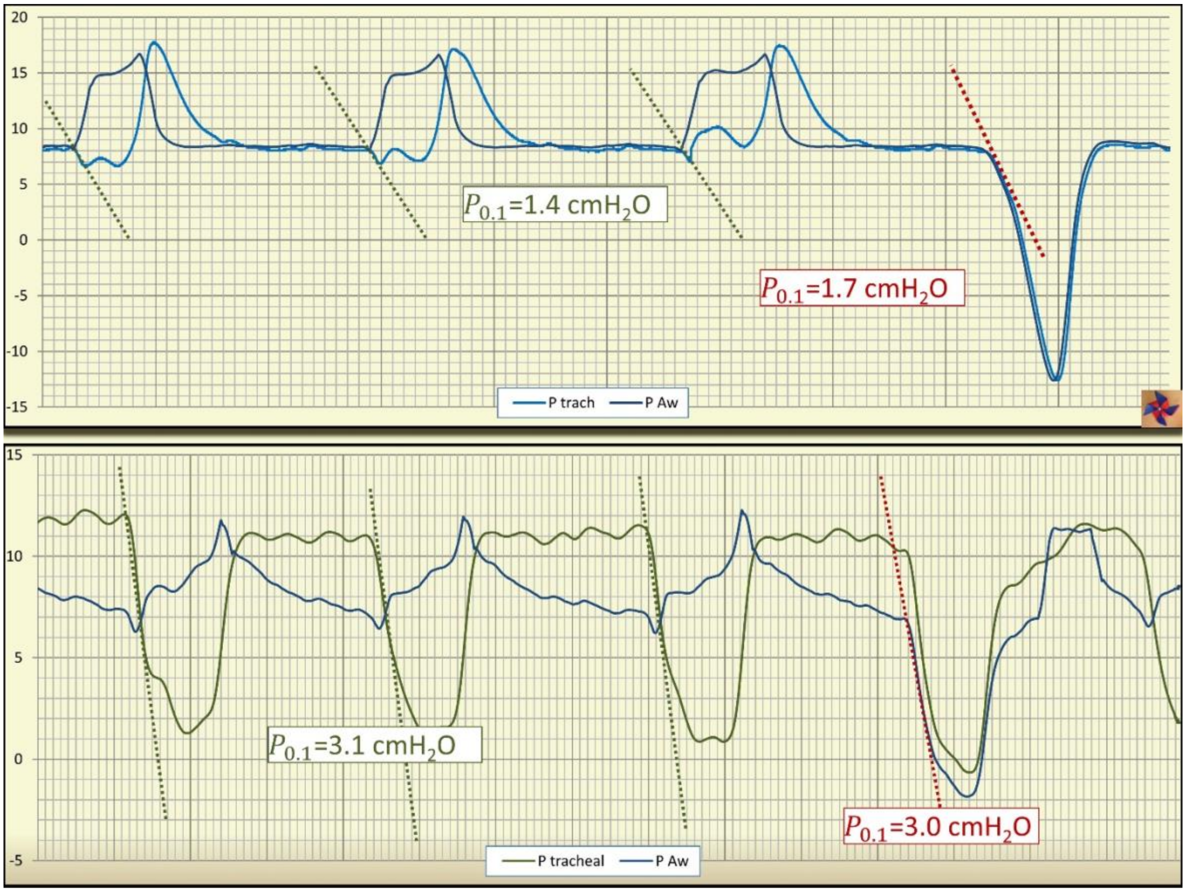

Figure 1

RecruitmEnt Assessed by eleCtRical Impedance Tomography (RECRUIT study)

Preliminary findings in a cohort of COVID-19 ARDS patients

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Introduction

Defining the potential for lung recruitment is a crucial aspect of safe positive end-expiratory pressure (PEEP) selection in mechanically ventilated patients, however no valid method exists to define the best PEEP. Moreover, COVID-19 patients exhibit complex physiological abnormalities affecting both ventilation and perfusion, likely making them more vulnerable to injury and harm from insufficient PEEP. By using electrical impedance tomography (EIT), we aim to determine the potential beneficial and harmful physiological effects of PEEP in patients with COVID-19 related acute respiratory distress syndrome (ARDS).

Method

In this observational study from the PLUG group (NCT04460859) we enrolled COVID-19 patients with moderate and severe ARDS in Toronto, Sao Paulo and Barcelona. EIT recordings, ventilator data and arterial blood gases were obtained during lung (de)recruitment maneuvers. PEEP was set to 6, 16 and 24 cmH_2O for 5-min per step, after which a decremental PEEP titration from 24 to 6 cmH_2O (in steps of 2 cmH_2O) was performed. Ventilator recruitment-to-inflation (R/I) ratio was calculated at 16 cmH_2O PEEP. With dedicated software we assessed lung collapse, overdistension and respiratory system compliance (Crs) at each PEEP step, and determined the PEEP level at the intercept of the relative overdistention and collapse curves during a decremental PEEP trial (Costa approach).

Results

This is a preliminary analysis in 45 patients (male/female: 31/14; age: 58±12y; BMI: 31±6.6 kg/m^2; P/F ratio at admission: 127±38 mmHg; baseline clinical PEEP: 11.8±3.0 cmH_2O). 89% (40/45) of patients tolerated PEEP increments up to 24 cmH_2O. When comparing PEEP 6 vs. 16 cmH_2O, the percentage collapse reduced (34.3±14.5% vs. 13.2±10.4%, $P<0.001$), overdistention increased (1.5±2.0% vs. 22.8±14.8%, $P<0.001$), and Crs did not change (29.6±8.9 vs. 29.3±7.9 mL/cmH_2O, $P=0.76$). Mean R/I ratio was 0.91, with large variability (SD: 0.45, min-max: 0.32-2.57). P/F ratio increased with higher PEEP (109±41, 144±50 and 230±96 mmHg for PEEP 6, 16 and 24 cmH_2O, respectively, $P<0.001$). At PEEP 24 cmH_2O this was associated with increases in overdistention ($P=0.03$). A decremental PEEP trial indicated that the median optimal PEEP as per the Costa approach was 14 [min-max: 5-19] cmH_2O. This PEEP level was different for those patients with a higher vs. lower than median increase in P/F ratio when going from 6 to 16 cmH_2O PEEP (15±1.9 vs. 11.8±3.4 cmH_2O, $P=0.003$).

Conclusion

In a subgroup of COVID-19 patients, recruitability varies and EIT data may indicate potential beneficial effects of higher PEEP levels. Ongoing work includes assessment of pressure-volume characteristics at different PEEP steps, development of an EIT-based recruitability index, and further correlations of EIT findings with clinical and ventilatory parameters.