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PHYSIOLOGICAL EFFECTS OF AN OPEN LUNG VENTILATORY STRATEGY TITRATED ON ELASTANCE-DERIVED END-INSPIRATORY TRANSPULMONARY PRESSURE: study in a pig model

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Running title: Transpulmonary pressure and open lung approach

ABSTRACT

Rationale: In presence of increased chest wall elastance the airway pressure does not reflect the lung-distending (transpulmonary) pressure.

Objective: to compare the physiological effects of a conventional open lung approach titrated for an end-inspiratory airway opening plateau pressure (30 cmH₂O) with a transpulmonary open lung approach titrated for a elastance-derived end-inspiratory plateau transpulmonary pressure (26 cmH₂O), in a pig model of ARDS (HCl inhalation) and reversible chest wall mechanical impairment (chest wall and abdomen restriction).

Methods: in eight pigs physiological parameters and computed tomography were recorded under three conditions: 1) conventional open lung approach, normal chest wall; 2) conventional open lung approach, stiff chest wall and 3) transpulmonary open lung approach, stiff chest wall.

Measurements and Main Results: as compared with the normal chest wall condition, at end-expiration non-aerated lung tissue weight increased by 116 ± 68 % during the conventional open lung approach and by 28 ± 41 % during the transpulmonary open lung approach ($p < 0.01$) whereas cardiac output decreased by 27 ± 19 % and by 22 ± 14 %, respectively ($p = \text{NS}$).

Conclusion: In this model, the end-inspiratory transpulmonary open lung approach minimized the impact of chest wall stiffening on alveolar recruitment without causing hemodynamic impairment.

INTRODUCTION

Conventional ventilatory treatment is titrated on airway opening pressure (P_{AO}) based on the assumption that P_{AO} closely approaches transpulmonary pressure (P_L), i.e. the difference between airway opening pressure (P_{AO}) and pleural pressure (P_{PL}). While this assumption is reasonable for patients with normal chest wall elastance (E_{CW}), in the presence of a substantial increase of the E_{CW} a relevant portion of P_{AO} is dissipated to distend the chest wall, leading to a lower than expected P_L . This may be clinically relevant in patients with ARDS since several studies consistently report that E_{CW} could be increased, due to intra-abdominal hypertension, pleural effusion, fluid overload and body wall edema (1). In these patients, targeting P_L rather than P_{AO} would be important (2-4). Recently Talmor et al., proposed a protocol to optimize the P_L at end expiration independently from the presence of impairment of E_{CW} (5).

The “open lung” approach aims at the best compromise between alveolar recruitment and over-distension, e.g. at the highest positive end-expiratory pressure (PEEP) level compatible with the absence of end-inspiratory alveolar hyperinflation. Despite three large clinical trials comparing the open lung with the conventional ARDS Network trial approach (6) (ExPress (7), ALVEOLI (8) and LOVS (9)) did not show any beneficial effecting terms of mortality, a recent meta-analysis suggests that the open lung approach improves mortality in patients with severe ARDS (10) and clinical guidelines suggest to use the open lung as a rescue ventilatory approach in patients with severe hypoxemia (11). In the ExPress trial (7), PEEP was set as high as possible to match an airway opening end-inspiratory plateau pressure ($P_{AO,PLAT}$) target of 30 cm H₂O, with the aim of fully exploiting the potential for alveolar recruitment. We reasoned that, in analogy with that protocol, in patients with impaired E_{CW} it would be more appropriate to match an end-inspiratory *transpulmonary* plateau pressure ($P_{L,PLAT}$) target, expression of the real end inspiratory lung distending pressure (or “stress”). Since in patients with ARDS and normal chest wall mechanics, E_{CW} represents the 15-20 % of respiratory system elastance (E_{RS}) (4, 12, 13), in these patients a $P_{AO,PLAT}$ of 30 cm H₂O corresponds to a *elastance-derived* $P_{L,PLAT}$ of 24-26 cmH₂O (see methods)

(13). Based on this assumption we set up the hypothesis that a *elastance-derived* $P_{L,PLAT}$ of 24 – 26 cmH₂O could be the target for an end-inspiratory transpulmonary open lung approach aiming at the same degree of end-inspiratory lung distending pressure (or “stress”) that would be obtained applying the ExPress trial protocol (7) in patients with normal chest wall mechanics.

To test our hypothesis, we compared in a large animal model of ARDS and reversible chest and abdomen restriction the conventional P_{AO} -based open lung approach (P_{AO} OLA) of the ExPress trial protocol (7) with a transpulmonary open lung approach based on PEEP titration to match a *elastance-derived* $P_{L,PLAT}$ target of 26 cm H₂O (P_L OLA).

METHODS (additional details provided in the online supplement)

Eight certified healthy mixed breed domestic pigs (weight 35 ± 3.6 kg) were studied, after approval by the Italian Ministry of Health's Ethical Committee (02/2010 – A, Roma, Italy). Animals were anesthetized, muscle paralyzed and mechanically ventilated with a Servo Ventilator 300 (Maquet, Solna, Sweden). Arterial blood gases, mean systemic arterial pressure (MAP) and right atrial pressure (RAP) were measured. Cardiac output (CO), intrathoracic blood volume (ITBV) and extra-vascular lung water index (EVLWI) were determined through the trans-pulmonary thermodilution technique (PiCCO[®], Pulsion Medical Systems, Munich, Germany) (14, 15). Derived hemodynamic parameters were calculated through standard formulae. Flow and P_{AO} were measured proximally to the endotracheal tube. Pleural (P_{PL}) and intra-abdominal pressures (IAP) were estimated using respectively esophageal pressure (P_{ES}) (16, 17) and gastric pressure (P_{GA}) (18) as surrogates, through a polyfunctional catheter (Nutrivent-Sidam, Mirandola, Italy) that incorporates in the lower part two thin walled polyethylene balloons (each 10 cm long and 15 mm diameter) (19). Each balloon was connected to a pressure transducer (Special Instruments Digima-Clic \pm cmH₂O; Nordlingen, Germany). Correct positioning of the balloons was verified as previously described (5, 20, 21).

Total positive end expiratory pressure ($PEEP_{TOT}$), $P_{AO,PLAT}$ and E_{RS} , E_L and E_{CW} , were measured as previously described (22).

The *elastance-derived* P_L was calculated, according to Gattinoni et al (13, 23). This method assumes that the ratio between E_L and E_{CW} determines how the pressure applied to the entire respiratory system (i.e. P_{AO}) is partitioned between the lung (determining P_L) and the chest wall (determining P_{PL}). For example, if E_L and E_{CW} contribute for 80% and 20% respectively to E_{RS} , in a passive patient 30 cmH₂O applied at the airway opening will generate a *elastance-derived* P_L of 24 cmH₂O (80% of P_{AO}) and a *elastance-derived* P_{PL} of 6 cmH₂O (20% of P_{AO}), respectively (13). The *elastance-derived* P_L represents the average transpulmonary pressure that, if applied to the

whole lung, would result in the observed lung volume in static conditions. By definition, it must be equal to zero at functional residual capacity (i.e. at zero P_{AO}), otherwise the lung would further empty (for a P_L lower than zero) or would further inflate (for a P_L higher than zero). Accordingly, also the *elastance-derived* P_{PL} ($P_{PL} = P_L - P_{AO}$) must be zero at functional residual capacity. Based on this background, the Gattinoni method (13) allows calculating the *elastance-derived* P_{PL} in static conditions in a passive patient submitted to positive pressure ventilation as follows:

$$(\Delta P_{PL}/\Delta V) / (\Delta P_{AO}/\Delta V) = E_{CW} / E_{RS} \quad (\text{equation 1})$$

and hence

$$\Delta P_{PL}/\Delta P_{AO} = E_{CW} / E_{RS} \quad (\text{equation 2})$$

By definition, the *elastance-derived* $P_{PL} - P_{AO}$ relationship described by equation 2 (whose slope is defined by the E_{CW} / E_{RS} ratio) must originate from zero at functional residual capacity, being P_{PL} and P_{AO} both equal to zero. Therefore, equation 2 can be rearranged as:

$$P_{PL} = P_{AO} * E_{CW}/E_{RS} \quad \text{Equation 3}$$

In summary, in this study we used tidal P_{ES} excursion to calculate E_{CW} (22) and the equation 3 to calculate the *elastance-derived* absolute P_{PL} at end expiration ($P_{PL,EXP}$) and at end inspiration ($P_{PL,PLAT}$). The *elastance-derived* P_L was finally calculated at end-expiration ($P_{L,EXP} = PEEP_{TOT} - P_{PL,EXP}$) and at end-inspiration ($P_{L,PLAT} = P_{AO,PLAT} - P_{PL,PLAT}$).

The shape of P_{AO} vs. time during constant flow inflation (*stress index*) was recorded and analyzed as previously described (24-27).

Frontal tomograms and helical CT scans of the chest were obtained. The following lung compartments were identified based on the “CT-number”, measured in Hounsfield Units (HU): *hyperinflated* (pixels with CT numbers between -1000 and - 900 HU); *poorly aerated* (between -

900 and - 500 HU); *normally aerated* (between - 500 and - 100 HU); *non-aerated* (between -100 and +100 HU) (13, 28-30). For each lung compartment, the weight of the corresponding lung tissue was calculated (31).

Protocol

For the entire experimental procedure the animals were ventilated in supine position. After the induction of an ARDS-like lung injury by instillation of hydrochloride (HCl) (32), stabilization was allowed for 1 h while ventilating the animals in a controlled constant-flow mode with a tidal volume (VT) of 10 ml/kg, an inspiratory to expiratory (I:E) ratio of 1:2, a respiratory rate (RR) of 20 breaths/min an inspired oxygen fraction (FiO₂) of 1, and zero end-expiratory pressure (ZEEP). Subsequently, chest wall and abdomen were strapped with two nearly inelastic cloth corsets (25 cm long each) with adjustable straps. In addition, two rectangular pneumatic cuffs (20 X 30 cm) were placed between the corset and the ventral part of abdomen and chest wall, respectively (33-35). The straps of the corsets were adjusted to that respiratory excursions were not hampered when the pneumatic cuffs were deflated. In order to increase E_{CW} (*Stiff Chest Wall* experimental conditions, see below) the pneumatic cuffs were inflated to a pressure of 20 cmH₂O (34, 35). Animals received a continuous infusion of maintenance fluid (lactated Ringer's solution, 10 ml/Kg/h); additional fluids and catecholamine infusions were not allowed.

Three ventilatory protocols were applied for 3 hours in a random order (concealed allocation, opaque sealed envelopes containing the randomization schedule). Measurement of respiratory mechanics, gas exchange, hemodynamics and thoracic CT scans at end-expiration and at end-inspiration were obtained after 3 h of application of each experimental condition.

Conventional open lung approach (P_{AO} OLA), Normal Chest Wall

Maintaining the pneumatic cuffs deflated, a lung recruiting maneuver (LRM) (continuous positive airway pressure 40 cmH₂O for 40 s) (3) was applied and subsequently pigs were ventilated

according to the Mercat open-lung protocol (7): $VT = 6$ ml/kg body weight, I:E = 1:2, RR in order to keep arterial pH between 7.30 and 7.45 up to maximum 35 breaths/min and PEEP individually set as high as possible to match a $P_{AO,PLAT}$ target of 30 cmH₂O. The FiO_2 was titrated in order to obtain a PaO_2 between 55 and 80 mmHg.

Conventional open lung approach (P_{AO} OLA), Stiff Chest Wall

After inflating the pneumatic cuffs, a LRM (continuous positive airway pressure 40 cmH₂O for 40 s) (3) was performed and the Mercat open lung ventilatory protocol was implemented (7).

Transpulmonary open lung approach (P_L OLA), Stiff Chest Wall

After inflating the pneumatic cuffs, a P_L -titrated LRM (continuous positive airway pressure to obtain a P_L of 35 cmH₂O for 40 s) was applied and, subsequently, PEEP was individually set to match a $P_{L,PLAT}$ target of 26 cmH₂O, regardless the resulting $P_{AO,PLAT}$. All the other ventilatory parameters were set according to the Mercat ventilatory protocol (7).

Statistical analysis

Normal distribution of the experimental data was evaluated by means of the Shapiro-Wilks test. Data are reported as mean \pm standard deviation. Data obtained in the different experimental ventilation conditions were compared by the analysis of variance (ANOVA) for repeated measure. If significant, a Student's t test for paired data with Bonferroni correction for post-hoc multiple comparisons was applied for evaluating the differences between each experimental conditions and the others. Significance was established at $p < 0.05$ for the ANOVA procedure and at $p < 0.0167$ for post-hoc multiple comparisons. Statistical analysis was carried out using the software package MedCalc (www.medcalc.org).

RESULTS

Table 1 and Figure 1 show the respiratory mechanics and gas exchange parameters recorded in the three experimental conditions. Compared to the P_{AO} OLA *Normal Chest Wall* condition, chest wall and abdomen restriction increased E_{CW} by $197 \pm 89\%$ during the P_{AO} OLA *Stiff Chest Wall* and by $179 \pm 85\%$ during the P_L OLA *Stiff Chest Wall* condition, respectively ($p = NS$ between the two *Stiff Chest Wall* conditions). During the P_{AO} OLA *Stiff Chest Wall* condition PEEP was set at 10 ± 2.6 cmH₂O and the resulting $P_{L,PLAT}$ was 19.5 ± 1.9 cmH₂O. During the P_L OLA *Stiff Chest Wall* condition, in order to match the $P_{L,PLAT}$ target, PEEP was increased to 20.5 ± 2.6 cmH₂O and the resulting $P_{AO,PLAT}$ was 39.4 ± 3.1 cmH₂O (Figure 1). The *stress index* was significantly lower in the P_{AO} OLA *Stiff Chest Wall* condition than in both the P_{AO} OLA *Normal Chest Wall* and the P_L OLA *Stiff Chest Wall* conditions (Table 1).

Arterial oxygenation significantly deteriorated going from the P_{AO} OLA *Normal Chest Wall* to the P_{AO} OLA *Stiff Chest Wall* condition. Maintaining $P_{L,PLAT}$ in the target range (P_L OLA) significantly improved oxygenation (Table 1). Of note, PaCO₂ was significantly higher during the P_{AO} OLA *Stiff Chest Wall* condition as compared with the P_{AO} OLA *Normal Chest Wall* and the P_L OLA *Stiff Chest Wall* conditions (Table 1).

Figure 2 displays representative CT images for the three ventilation conditions acquired at end-expiration at the apex, carina and base level. To allow a quantitative estimation of lung tissue attenuation properties, images were read based on the color-coding table UCLA (OsiriX image processing software, Geneva, Switzerland). At all the three levels, non-aerated lung areas (color coded in red-yellow) were significantly more represented during the P_{AO} OLA *Stiff Chest Wall* condition. Maintaining $P_{L,PLAT}$ in the target range clearly decreased the amount of non-aerated lung areas and increased the amount of normally aerated lung areas (color coded in blue). Table 2 reports the total weight of hyperinflated, normally aerated, poorly aerated and non-aerated lung compartments under each experimental ventilation condition. Figure 3 shows the lung tissue weight

of each of the four lung compartments, at end-expiration under each experimental ventilation condition, expressed as percentage of total lung tissue weight.

Table 3 reports the main hemodynamic parameters. Chest wall and abdomen restriction significantly decreased CO, stroke volume (SV) and ITBV, without significant differences between the P_{AO} OLA *Stiff Chest Wall* and P_L OLA *Stiff Chest Wall* condition (Table 3).

DISCUSSION

The main finding of this study is that, in a model of ARDS and concomitant chest wall mechanical impairment, titrating the open lung strategy on $P_{AO,PLAT}$ results in lung derecruitment and severe hypoxemia while, on the other hand, titrating PEEP to target a *elastance-derived* $P_{L,PLAT}$ of 26 cmH₂O improves lung recruitment and oxygenation without worsening hemodynamics and inducing significant alveolar hyperinflation.

We show that the performance of a well known open lung protocol (7) may be biased by chest wall and abdomen restriction. Several studies have shown that commonly applied PEEP levels are insufficient to counteract the functional residual capacity decline induced by impaired E_{CW} (12, 36, 37). Kubiak and coworkers recently showed in a pig model that increasing IAP causes a progressive increase in $P_{AO,PLAT}$, whereas $P_{L,PLAT}$ remains unchanged (38). Overall, our data confirm the assumption that $P_{AO,PLAT}$ is a poor indicator of lung distension in the setting of abnormal E_{CW} .

In clinical practice P_{ES} , measured in the lower third of the esophagus through an air-inflated balloon, is the main surrogate for P_{PL} (2). Indeed, the real P_{PL} varies from place to place in the pleura and is influenced by gravity, weight of mediastinal organs and of the abdominal content and lung inflation status (2, 39). As recently elucidated by Loring et al (39), two main methods have been proposed for translating the absolute P_{ES} value read in the lower third of the esophagus into a meaningful P_{PL} value: a) Talmor et al proposed to use the absolute P_{ES} itself, after subtracting 5 cmH₂O as a correction to compensate for the gravitational change in P_{PL} due to the weight of mediastinal content in the supine patient (*measured* P_{PL}) (5, 20); b) Gattinoni et al, proposed to use the ratio between E_L and E_{CW} to determine how the pressure applied to the entire respiratory system (i.e. P_{AO}) is partitioned between the lung (determining P_L) and the chest wall (determining P_{PL}) the *elastance-derived* P_L and P_{PL} , respectively) (13, 23). As explained in the method section, by definition both the *elastance-derived* P_{PL} and P_L are zero at functional residual capacity and must be

positive when PEEP is applied whereas, of note, the *measured* $P_{PL,EXP}$, has been found to be higher than zero, implying a negative *measured* $P_{L,EXP}$, in several ARDS patients (20). Loring et al explained this apparent paradox (a negative $P_{L,EXP}$ should promote lung emptying) by considering that the small airways of collapsed dependent lung regions (that correspond to the lower third of the esophagus where P_{ES} is measured) could be closed and/or contain fluids that prevent alveolar pressure from equilibrating to airway pressure (40). They demonstrated that *elastance-derived* P_L overestimates *measured* P_L because, at variance with *elastance-derived* P_{PL} , *measured* P_{PL} takes into account the eventual surplus of pressure acting on the dependent lung at end-expiration (39), a condition that is clinically relevant and may promote lung atelectasis, particularly in the dependent lung regions, when IAP is increased (1). In a recent clinical study on patients with ARDS, Talmor et al used *measured* $P_{L,EXP}$ ($PEEP - \textit{measured } P_{PL,EXP}$) to titrate PEEP in order to achieve a positive $P_{L,EXP}$ (between 0 and 10 cmH₂O according to a $P_{L,EXP} / FiO_2$ oxygenation table), obtaining a significant improvement of oxygenation and lung compliance and a trend towards improved survival (5). The same approach reduced ventilator-induced lung injury (VILI) in a murine model of ARDS and chest wall restriction (40). Despite these important findings, several experts raised doubts that the *measured* P_{PL} could be used as a surrogate for the P_{PL} acting on the whole lung during mechanical ventilation and suggested to perform further studies to better define the method to translate absolute P_{ES} into a physiologically sound P_{PL} value (2, 41-43). Accordingly, we set up the hypothesis that titrating PEEP to target the *elastance-derived* $P_{L,PLAT}$ of 26 cmH₂O, based on the rationale of the ExPress trial (7), could be an alternative transpulmonary "open lung" approach. Our data suggest that it could be advantageous in terms of gas exchange and lung recruitment. Furthermore, we recently applied the same strategy in 14 patients with Influenza A (H1N1)-induced ARDS candidate to extracorporeal membrane oxygenation (ECMO) and were able to reverse hypoxemia refractory to the conventional PAO OLA in 7 of them (44). However we point out that our experimental and clinical findings, obtained in an animal model and in a small cohort of patients, need to be further confirmed.

The P_L OLA may raise concerns of venous return impairment. Confirming the results of previous studies (3, 36), in our model the association between increased IAP and high PEEP levels significantly reduced CO and ITBV (Table 3) suggesting a decrease in venous return, as previously demonstrated by Takata and coworkers (45). Of note, however, the impairment in ITBV and CO was similar in the P_{AO} OLA and P_L OLA *Stiff Chest Wall* conditions, despite the higher P_{AO} levels applied to realize the P_L OLA. In order to explain these findings, we speculate that the significant alveolar recruitment and the corresponding increase in lung volume in the P_L OLA condition could have in part relieved the compression exerted by the chest wall on the mediastinal structures.

Both chest wall stiffening and the open lung ventilatory strategy may affect right ventricular function (46). The overall effect depends on the interplay between several parameters, including PEEP-induced alveolar recruitment *and/or* hyperinflation, preload status, fluid loading, hypercapnia (46-50). Unfortunately we did not directly evaluate right ventricular function, but, since we did not observe significant differences in CO going from the P_{AO} OLA to the P_L OLA *Stiff Chest Wall* condition, we speculate that the P_L OLA *per se* did not impair right ventricular function.

Confirming the results of a previous study (51), the P_{AO} OLA *Normal Chest Wall* ventilation condition induced a small but detectable degree of alveolar hyperinflation (3.8 ± 1.8 % of total lung weight at end-expiration and 5.3 ± 1.6 % at end-inspiration) (Table 2, Figure 3). The amount of alveolar hyperinflation significantly decreased during the P_{AO} OLA *Stiff Chest Wall* condition, whereas it returned similar to the P_{AO} OLA *Normal Chest Wall* condition during the P_L OLA *Stiff Chest Wall*. Interestingly both the *stress index* (26) and the end-inspiratory stress posed on the whole lung, as expressed by the $P_{L,PLAT}$, were significantly higher in the P_{AO} OLA *Normal Chest Wall* and in the P_L OLA *Stiff Chest Wall* conditions than in the P_{AO} OLA *Stiff Chest Wall* condition (Table 1). However, probably due to the limited amount of hyperinflation, the *stress index* remained in the range indicating absence of tidal alveolar mechanical stress (i.e. between 0.9 and 1.1) (25, 27) in all the experimental conditions (Table 1). Overall, our results seem in line with a recent study by Chiumello and coworkers showing that the degree of tidal mechanical stress is

correlated with $P_{L,PLAT}$ rather than with $P_{AO,PLAT}$ (12) and with a previous experimental study by Hernandez and coworkers showing that chest wall restriction limits airway pressure induced lung injury (52).

Limitations. *First:* we used a large animal model consistently shown to mimic human ARDS (32, 51) but the results of animal studies need to be extrapolated to the human context with extreme caution. *Second:* the method used in the present study to increase chest wall and abdomen elastance, although validated in the human context (33-35), to our knowledge was not previously tested in pigs. *Third:* other open lung ventilatory approaches exist that do not limit the $P_{AO,PLAT}$ to 30 cmH₂O (53, 54). It is conceivable that targeting a $P_{L,PLAT}$ higher than 26 cmH₂O would have been even more advantageous in terms of alveolar recruitment. On the other hand, recent evidences suggest that alveolar hyperinflation may occur even at $P_{AO,PLAT}$ as low as 28-30 cmH₂O (26, 55). Accordingly, despite the fact that in the present study we recorded a small degree of alveolar hyperinflation and the stress index remained in the normal range, it is possible that the P_L OLA could induce alveolar hyperinflation in other experimental models or in patients. Furthermore, Protti and coworkers recently showed in healthy pigs ventilated without PEEP and with variable VTs (in order to reproduce different levels of strain, i.e. the ratio between VT and functional residual capacity) that ventilator induced lung injury may ensue at a delta P_L ($P_{L,PLAT} - P_{L,EXP}$) as high as 13.5 ± 5 cmH₂O corresponding to a strain of 2.16 ± 0.58 (56). The comparison with Protti's data and ours is biased by the fact that we studied lung-damaged pigs and that PEEP and chest restriction were applied. However in our pigs delta P_L were slightly lower than those recorded by Protti in pigs developing VILI (11.8 ± 1.8 ; 12.3 ± 2 and 11.8 ± 1.7 cmH₂O in the PAO OLA normal Chest Wall, PAO OLA stiff chest wall and PL OLA stiff Chest Wall condition, respectively; $P = NS$). Overall, we point out that further studies are needed to define the ideal $P_{L,PLAT}$ target and that the available data strongly suggest that lung mechanical stress should be ideally always monitored when ventilating ARDS patients (26, 55).

In conclusion, we show that taking into account the end-inspiratory *elastance-derived* transpulmonary pressure in the setting of ARDS and chest wall mechanical impairment improves lung recruitment and oxygenation without causing hemodynamic impairment and alveolar hyperinflation. Despite one may argue that the results of this study are concordant with physiological expectations, our aim was defining a ventilatory protocol suitable for clinical application. Indeed, despite the large body of theoretical knowledge, the ventilatory treatment is titrated on P_{AO} in the vast majority of ARDS patients, clearly indicating the need of translating physiology into ventilatory protocols. From this point of view, our data clearly suggest that, since it is impossible to predict what is the real transpulmonary pressure, it should be measured in all ARDS patients.

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FIGURE LEGENDS

FIGURE 1: values of *elastance-derived* end-inspiratory plateau airway opening, transpulmonary and pleural pressure ($P_{AO,PLAT}$, $P_{L,PLAT}$ and $P_{PL,PLAT}$) recorded during a 3 – 5 sec end-inspiratory occlusion, under each experimental condition. By protocol, during the conventional open lung approach (P_{AO} OLA), PEEP was titrated to match a $P_{AO,PLAT}$ of 30 cmH₂O. During the *Stiff Chest Wall* condition positive end-expiratory pressure (PEEP) was significantly reduced as compared with the *Normal Chest Wall* condition, in order to match the $P_{AO,PLAT}$ target. Being the chest wall stiffer, a higher portion of pressure applied at the airway opening was dissipated to expand the chest wall leading to a higher $P_{PL,PLAT}$ and to a lower $P_{L,PLAT}$. To realize the alternative transpulmonary open lung approach (P_L OLA), PEEP was titrated to match a *elastance-derived* $P_{L,PLAT}$ target of 26 cmH₂O, regardless the resulting $P_{AO,PLAT}$. The dotted lines indicate the pre-defined targeted $P_{L,PLAT}$ range. Of note, during the P_{AO} OLA *Normal Chest Wall* condition $P_{L,PLAT}$ was almost exactly in the targeted range.

Data are expressed as mean \pm standard deviation.

* $p < 0.05$ versus P_{AO} OLA Normal Chest Wall;

† $p < 0.05$ versus P_{AO} OLA Stiff Chest Wall.

FIGURE 2: Representative CT images acquired under each experimental ventilation condition at end-expiration at three levels: 1) apex; 2) carina and 3) at a level resulting in the largest transverse lung section between the most cranial point of the diaphragm and the base of the heart (base). In order to allow a “qualitative” estimation of lung tissue attenuation properties, images were read based on the color-coding table “UCLA” (OsiriX image processing software, <http://www.osirixfoundation.com>, Geneva, Switzerland). The conventional open lung approach (P_{AO} OLA) was applied in *Normal Chest Wall* condition and following chest wall restriction in

order to increase chest wall elastance (E_{CW}) (*Stiff Chest Wall* condition). Non-aerated lung areas (color coded in red-yellow) significantly increased in the P_{AO} OLA *Stiff Chest Wall* ventilation condition. Maintaining *elastance-derived* $P_{L,PLAT}$ in the target range (P_L OLA) clearly decreased the amount of non-aerated lung areas and increased the amount of normally aerated lung areas (color coded in blue).

HU = Hounsfield units; $P_{AO,PLAT}$ = end-inspiratory plateau airway opening pressure, $P_{L,PLAT}$ = end-inspiratory plateau transpulmonary pressure; PEEP = positive end-expiratory pressure.

FIGURE 3: Graph depicting lung tissue weight of each of the four lung compartments, at end-expiration under each experimental ventilation condition, expressed as percentage of total lung tissue weight. Lung compartments were identified based on degree of aeration, as expressed by the “CT-number”, measured in Hounsfield Units (HU): *hyperinflated* (pixels with CT numbers between -1000 and - 900 HU); *poorly aerated* (between - 900 and - 500 HU); *normally aerated* (between - 500 and - 100 HU); *non-aerated* (between -100 and +100 HU).

P_{AO} OLA = airway opening pressure based open lung approach; P_L OLA = transpulmonary pressure based open lung approach.

Data are expressed as mean \pm standard deviation. * $p < 0.05$ versus P_{AO} OLA Normal Chest Wall; † $p < 0.05$ versus P_L OLA Stiff Chest Wall.