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Opening pressures and atelectrauma in acute respiratory distress syndrome

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Abstract

Purpose: Open lung strategy during ARDS aims to decrease the ventilator-induced lung injury by minimizing the atelectrauma and stress/strain maldistribution. We aim to assess how much of the lung is opened and kept open within the limits of mechanical ventilation considered safe (i.e., plateau pressure 30 cmH_2O, PEEP 15 cmH_2O).

Methods: Prospective study from two university hospitals. Thirty-three ARDS patients (5 mild, 10 moderate, 9 severe without extracorporeal support, ECMO, and 9 severe with it) underwent two low-dose end-expiratory CT scans at PEEP 5 and 15 cmH_2O and four end-inspiratory CT scans (from 19 to 40 cmH_2O). Recruitment was defined as the fraction of lung tissue which regained inflation. The atelectrauma was estimated as the difference between the intratidal tissue collapse at 5 and 15 cmH_2O PEEP. Lung ventilation inhomogeneities were estimated as the ratio of inflation between neighboring lung units.

Results: The lung tissue which is opened between 30 and 45 cmH_2O (i.e., always closed at plateau 30 cmH_2O) was 10 ± 29, 54 ± 86, 162 ± 92, and 185 ± 134 g in mild, moderate, and severe ARDS without and with ECMO, respectively ($p < 0.05$ mild versus severe without or with ECMO). The intratidal collapses were similar at PEEP 5 and 15 cmH_2O (63 ± 26 vs 39 ± 32 g in mild ARDS, $p = 0.23$; 92 ± 53 vs 78 ± 142 g in moderate ARDS, $p = 0.76$; 110 ± 91 vs 89 ± 93, $p = 0.57$ in severe ARDS without ECMO; 135 ± 100 vs 104 ± 80, $p = 0.32$ in severe ARDS with ECMO). Increasing the applied airway pressure up to 45 cmH_2O decreased the lung inhomogeneity slightly (but significantly) in mild and moderate ARDS, but not in severe ARDS.

Conclusions: Data show that the prerequisites of the open lung strategy are not satisfied using PEEP up to 15 cmH_2O and plateau pressure up to 30 cmH_2O. For an effective open lung strategy, higher pressures are required. Therefore, risks of atelectrauma must be weighted versus risks of volutrauma.

Trial registration: Clinicaltrials.gov identifier: NCT01670747 (www.clinicaltrials.gov).

Keywords: Volutrauma, Atelectrauma, ARDS, Lung recruitment, Opening pressure

Introduction

The lung protective strategy, in its original definition [1, 2], consisted of a combination of low tidal volume (TV) and high positive end-expiratory pressure (PEEP). This strategy found its conceptual background in three major sources. First, was a lung model by Mead [3], which described the theoretical distribution of stress and strain in an inhomogeneous lung. In these conditions, the interfaces of regions with different elasticity act as stress raisers leading to up to a fourfold multiplication of local pressures (a theoretical increase from 30 to 120 cmH_2O in a fully distended lung). The second conceptual source for the lung protective approach was the landmark editorial by Lachmann [4], "Open up the lung

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and keep the lung open", which, years later, popularized Mead's theory. Accordingly, the use of high PEEP would decrease lung inhomogeneity and prevent intratidal collapse and reinflation, a putative relevant mechanism for the occurrence of ventilator-induced lung injury (VILI) [5]. Finally, the biological plausibility for the open lung theory derives from experiments on isolated rat lungs, where higher PEEP decreased the production of inflammatory cytokines by keeping the lung open and preventing atelectrauma [6], later confirmed in patients with acute respiratory distress syndrome (ARDS) [7].

This paradigm went on substantially unchallenged over the years. Actually, the component of lung protection related to the low tidal volume has found consistent experimental [8, 9] and clinical support [10] in a structured, theoretical framework [11]. Consequently, the set tidal volume decreased worldwide from the 12–15 ml/kg in the 1970s [12] to the present average of 7.6 ml/kg, as recently documented in an international survey [13]. In contrast, the "open lung" component of the original protective lung strategy has not provided a convincing evidence of benefit. In fact, the first component of the open lung strategy (i.e., the recruitment maneuvers), essential for lung opening, neither reduced VILI nor improved outcome [14, 15], appearing in some studies more deleterious than useful [16]. The second component of the open lung strategy (i.e., higher PEEP) designed for keeping the lung open, failed, in large trials, to show any benefit compared to lower PEEP [17–19]. Moreover, the "asymptote" of the lung protective/open lung strategy in ARDS, which consists of ultra-low tidal volume associated with a PEEP level so high as to reach the near total lung capacity (i.e., the high-frequency oscillation ventilation, HFOV) not only did not provide benefits [20] but was even harmful [21].

Therefore, either the atelectrauma is less important than currently believed or the pressures currently used in the "higher PEEP" protocols are insufficient to prevent its occurrence. In this paper, in a series of 33 patients with ARDS of increasing severity, we aimed to assess whether the mechanical ventilation at 30 cmH_2O of plateau pressure and 15 cmH_2O of PEEP—as commonly applied in the "higher PEEP" protocols—actually "opens the lung and keeps it open".

Materials and methods

Thirty-three consecutive patients studied after a median of 3 (range 1–5) days of ARDS were classified as mild ($n = 5$), moderate ($n = 10$), and severe ($n = 9$ without ECMO and $n = 9$ with it) according to their PaO_2/FiO_2 ratio measured at 5 cmH_2O of PEEP [22]. Patients were studied between 2013 and 2015 in two university hospitals (Fondazione IRCCS Ca' Granda–Ospedale Maggiore Policlinico, Milan, Italy and Department of Intensive Care Medicine, Rebro Hospital, University of Zagreb, Croatia). The study was approved by the institutional review board of each hospital, and written consent was obtained according to the national regulations (Clinicaltrials.gov identifier: NCT01670747). Nine patients, all in Policlinico Hospital, where studied while undergoing veno-venous ECMO. Details about sedation, measurements, and protocol are available in the electronic supplementary material (ESM).

Pressure and volume measurements

All the airway pressures, the esophageal pressure, tidal volumes, and flows were continuously sampled at 100 Hz and processed on a dedicated data acquisition system (Colligo and Computo, www.elekton.it, Milan, Italy). Data presented are the ones measured with the calibrated acquisition system and not the ones set on the ventilator (set and measured values could differ by up to approximately 10%). For clarity, the results in the main manuscript are expressed as a function of the airway pressure. A complete set of results expressed as a function of the transpulmonary pressure is available in the ESM.

Inspiratory recruitment

Each patient underwent a CT scan in static conditions at 5 cmH_2O PEEP (end-expiration) and three further CT scans after applying inspiratory airway plateau pressures of 19 ± 2, 28 ± 0, and 40 ± 2 cmH_2O (see ESM for the rationale of the set pressures). At each airway plateau pressure the inspiratory recruitment was computed as the difference between uninflated tissue at PEEP and plateau pressure.

Intratidal opening/closing tissue

To quantify the intratidal opening and closing tissue (recruitment–derecruitment), each patient was ventilated with the same tidal volume (6–8 ml/kg IBW) at 5 and 15 cmH_2O PEEP. Whole-lung CT scans were performed in static conditions both at end-expiration (5 and 15 cmH_2O) and at corresponding plateau pressures at end-inspiration (19 ± 2 and 27 ± 3 cmH_2O, respectively). The recruited/derecruited tissue was computed as the difference between end-expiratory and end-inspiratory uninflated tissue at 5 and 15 cmH_2O PEEP.

CT scan analysis

The outline of the lungs was manually drawn in each CT section excluding the hilar vessels and the main bronchi. Segmented images were analyzed with custom dedicated software (Soft-E-Film, www.elekton.it, Milan, Italy). Lung tissue was classified according to its gas/tissue content as

uninflated (Hounsfield units between +100 and −100), poorly aerated (Hounsfield units number between −101 and −500), normally inflated (Hounsfield units number between −501 and −900), and hyperinflated (Hounsfield units number between −901 and −1000) [23]. We defined the recruitability as the difference between uninflated tissue at 5 and 45 cmH_2O, which we arbitrarily assumed to be the "full recruitment".

Lung inhomogeneities

The lung inhomogeneity was measured by comparing the inflation of neighboring lung regions: if two neighboring regions were perfectly "homogeneous" at a given pressure applied, their inflation should be similar and the inflation ratio of the two regions will be equal to one [24]. We defined the lung inhomogeneity threshold as the percentage of lung volume presenting an inflation ratio greater than 1.61 (95th percentile of a control population) [25].

Statistical methods

Data are presented, where not differently specified, as means ± standard deviations. Lung recruitment and lung inhomogeneity as a function of study step and severity of disease (according to the Berlin classification) were analyzed with a mixed effect model, and multiple comparisons were performed with the Benjamini, Hochberg, and Yekutieli method [26]. Intratidal collapse and reinflation between PEEP 5 cmH_2O and 15 cmH_2O were compared with paired *t* test. Statistical analysis was performed with R software [27].

Results

Table 1 summarizes the most relevant physiological and clinical characteristics of the patient population. According to a modified Berlin definition (i.e., assessing the PaO_2/FiO_2 ratio at PEEP 5 cmH_2O instead of at clinical PEEP) [22], 5 patients presented with mild, 10 with moderate, and 18 with severe ARDS (9 without ECMO

Table 1 Patients' characteristics

	Mild ($n = 5$)	Moderate ($n = 10$)	Severe No ECMO ($n = 9$)	Severe With ECMO ($n = 9$)	*p* value
Age (years)	59 ± 24	49 ± 12	59 ± 17	57 ± 12	0.45
Female, *n* (%)	2 (40%)	4 (40%)	2 (22%)	2 (22%)	0.77
Body mass index (kg/m^2)	27 ± 9	26 ± 6	28 ± 9	26 ± 3	0.91
Tidal volume/ideal body weight (ml/kg IBW)[b]	7.8 (1)	7.8 (1.2)	8.4 (1.5)	4.8 (1.4)*†‡	<0.0001
Minute ventilation (l/min)[a]	8 ± 1	9 ± 2	10 ± 2	4 ± 1*†‡	<0.0001
Respiratory rate (breaths/min)[a]	15 ± 2	18 ± 4	18 ± 4	11 ± 2†‡	<0.001
PEEP (cmH_2O)[a]	11 ± 2	10 ± 4	12 ± 3	14 ± 4†	0.04
Respiratory system elastance (cmH_2O/l)[b]	28 (9)	31 (5)	29 (12)	25 (17)	0.17
PaO_2/FiO_2[b]	242 ± 30	147 ± 27*	81 ± 18*†	87 ± 14*†	<0.0001
$PaCO_2$ (mmHg)[b]	44 ± 7	46 ± 6	45 ± 10	42 ± 6	0.67
Total lung tissue (g)	1237 ± 135	1485 ± 297	1761 ± 413	2258 ± 905*†	<0.01
Total gas (ml)	912 ± 640	940 ± 548	822 ± 229	586 ± 492	0.42
Uninflated tissue (%)	46 ± 4	40 ± 16	58 ± 9†	70 ± 11*†	<0.0001
Consolidated tissue (%)	35 ± 4	24 ± 15	36 ± 10	40 ± 20	0.11
Recruitable tissue (%)	10 ± 1	16 ± 9	22 ± 11	28 ± 15*	0.03
Poorly inflated tissue (%)	32 ± 7	39 ± 12	26 ± 7†	22 ± 9†	<0.01
Well-inflated tissue (%)	22 ± 9	20 ± 11	16 ± 6	8 ± 5*†	<0.01
Overinflated tissue (%)	0 ± 1	0 ± 0	0 ± 0	0 ± 0	0.25
ICU mortality *n* (%)	2 (40%)	5 (50%)	8 (89%)	2 (22%)	0.04
Cause of ARDS					
Pneumonia	0 (0%)	0 (0%)	6 (67%)	9 (100%)	<0.0001
Sepsis	3 (60%)	7 (70%)	2 (22%)	0 (0%)	<0.01
Trauma	1 (20%)	1 (10%)	0 (0%)	0 (0%)	0.37
Aspiration	0 (0%)	0 (0%)	1 (11%)	0 (0%)	0.43
Other	1 (20%)	2 (20%)	0 (0%)	0 (0%)	0.27

* $p < 0.05$ vs mild, † $p < 0.05$ vs moderate, ‡ $p < 0.05$ vs severe no ECMO

[a] Data refer to prestudy settings

[b] Data collected at PEEP 5 cmH_2O

and 9 with it). As shown, the majority of the patients had severe ARDS, as one of the two enrolling centers is a referral center for extracorporeal membrane oxygenation (ECMO). The main cause of ARDS in this population was pneumonia (15 patients, all presenting with severe ARDS), followed by extrapulmonary sepsis (12 patients, distributed through the different degrees of severity).

Inspiratory lung recruitment and opening pressure

Figure 1 shows a representative example of subsequent CT scans during inspiration in a patient with severe ARDS. As shown, recruitment and inhomogeneities occur along the whole pressure–volume curve. Figure 2 reports the average recruitment–pressure curves obtained in patients with mild, moderate, and severe ARDS (with and without ECMO). From this figure it is evident that (a) the total amount of recruitable tissue increases with ARDS severity and is largely different between mild, moderate, and severe ARDS at each applied inspiratory pressure; (b) the amount of recruitable tissue between 30 and 45 cmH_2O (set on the ventilator) was negligible in mild ARDS (10 ± 29 g, 8 ± 21%), modest in moderate ARDS (54 ± 86 g, 17 ± 27%), and much greater in severe ARDS, both without ECMO (162 ± 92 g, 43 ± 21%, $p = 0.02$ vs mild ARDS and $p < 0.0001$ vs moderate ARDS) and with ECMO (185 ± 134 g, 31 ± 12%, $p < 0.0001$ vs mild ARDS and $p < 0.0001$ vs moderate ARDS).

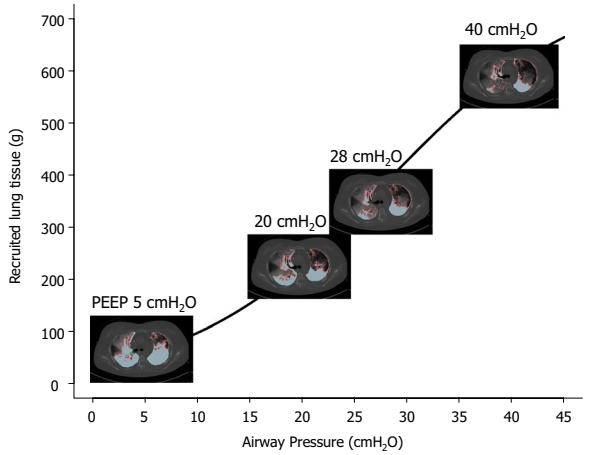

Fig. 1 A representative CT scan–pressure curve in a patient with severe ARDS. The shown CT scans are taken at hilum at 5 cmH_2O PEEP and at measured plateau pressures of 19.5, 30, and 45 cmH_2O plateau pressure set on the ventilator. The measured pressures may slightly differ from the set ones. Uninflated tissue is represented in *light blue*, inhomogeneous lung tissue in *red*. In this patient the uninflated tissue of the whole lung amounted to 1091 g at 5 cmH_2O and 812, 747, and 477 g at the indicated plateau pressures. Lung inhomogeneities were 20% at PEEP 5 cmH_2O and 20, 22, and 21% at the three plateau pressures. As shown, increasing the pressures, some inhomogeneities disappeared while new inhomogeneities appeared, resulting in a net unmodified total extent of approximately 20% in the whole lung

Collapse and reinflation

Table 2 reports the amount of uninflated tissue measured at 5 and 15 cmH_2O PEEP in mild, moderate, and severe ARDS (with and without ECMO). As shown, the lung tissue recruited between 5 and 15 cmH_2O (i.e., the difference between uninflated tissue at the two PEEP levels) is modest and not significant in mild ARDS (56 ± 50 g), increases significantly in moderate ARDS (116 ± 71 g), and amounted to 236 ± 202 g in severe ARDS without ECMO and to 231 ± 177 g in severe ARDS with ECMO.

The lower panel of Table 2 reports the amount of tissue which tidally opened and collapsed approximately 15 times per minute at PEEP 5 and 15 cmH_2O in mild, moderate, and severe ARDS ventilated with similar tidal volumes (6–8 ml/kg IBW). As shown, the amount of collapsing and decollapsing tissue increased from mild to moderate, to severe ARDS and, within the different severity classes, was not significantly different between PEEP 5 and 15 cmH_2O. The changes in gas exchange and in respiratory mechanics when increasing PEEP from 5 to 15 cmH_2O (according to the PEEP test performed in the ICU before the CT scan) are reported in the ESM.

Lung inhomogeneities

Table 3 reports the extent of lung inhomogeneities estimated in mild, moderate, and severe ARDS at the different end-inspiratory and end-expiratory pressures. As shown, (a) the extent of inhomogeneities increased (but not significantly) from mild to moderate and severe ARDS, at each tested pressure; (b) within the same class of severity, the decrease of lung inhomogeneity, increasing the plateau pressure, reached statistical significance in patients with moderate ARDS and in patients with severe ARDS with ECMO; (c) within the same class of severity, increasing PEEP from 5 to 15 cmH_2O reduced significantly the lung inhomogeneities in mild and moderate ARDS, while it did not change in the severe ARDS groups. The variability and the extent of the inhomogeneity variation with PEEP are evident in Fig. 3, where the changes of inhomogeneity in the single patients are represented. As shown, in some patients with moderate or severe ARDS, the increase of PEEP was associated with an increase in lung inhomogeneity.

Additional results

Inspiratory lung recruitment and opening/closing pressures as a function of transpulmonary pressure, as well as the relationships between airway and transpulmonary pressure, are reported in the ESM. A complete set of the

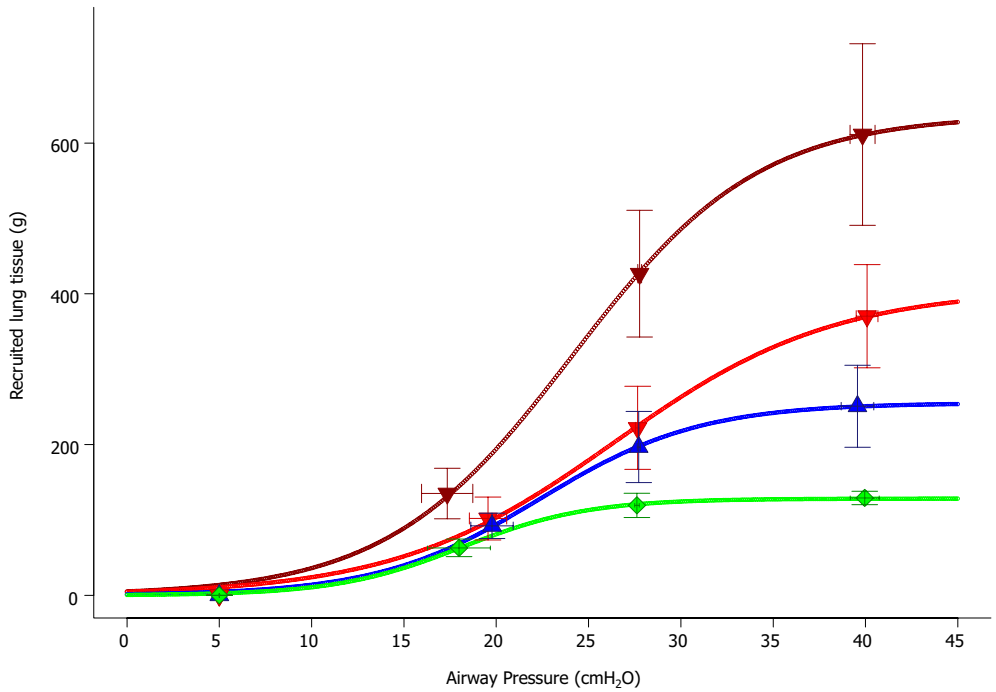

Fig. 2 Lung recruitment as a function of airway pressures in mild, moderate, and severe ARDS. Figure presents the grams of lung tissue which regain inflation (means and standard errors) as a function of the applied airway pressures. *Diamonds* represent mild ARDS, *upward triangles* moderate ARDS, and *downward triangles* severe ARDS (*light red* without ECMO, *dark red* with it). Lung recruitment was fitted with sigmoidal equations [uninflated tissue (grams) = $L/(1 + \exp(-k \times (\text{pressure } (\text{cmH}_2\text{O}) - x_0)))$]. Fitted coefficients were $L = 638$, $k = 0.20$, and $x_0 = 24$ for severe ARDS with ECMO; $L = 406$, $k = 0.17$, and $x_0 = 26$ for severe ARDS without ECMO; $L = 255$, $k = 0.23$, and $x_0 = 22$ for moderate ARDS; and $L = 128$, $k = 0.29$, and $x_0 = 18$ for mild ARDS). The indicated pressures on the *X* axis are the measured pressures, slightly different from the ones set on the ventilator. The inspiratory and expiratory points measured at 15 cmH_2O PEEP are excluded for sake of clarity: the expiratory points because the relationship describes the inspiratory recruitment and the inspiratory points because they are very close to the 28 cmH_2O points. The reader can find the values in eTables 1 and 2 (ESM)

CT scan data obtained in each of the experimental conditions is also reported in the ESM.

Discussion

In patients with early ARDS we found that (a) at 30 cmH_2O, a generally accepted threshold of safety for mechanical ventilation, 10–30% of the potentially recruitable lung tissue remains always closed in patients with moderate and severe ARDS; (b) ventilating a patient with a tidal volume of 6–8 ml/kg and 15 cmH_2O of PEEP is largely insufficient to prevent cyclic lung tissue opening and closing; (c) increasing PEEP decreased inhomogeneity by 3–4% of the total lung volume in mild and moderate ARDS, while in the severe ARDS groups it was unmodified.

These data must be discussed in the face of the putative benefits of the open lung strategy, for which (a) a full opening of the lung is necessary to minimize the interfaces between open and closed lung regions; (b) higher PEEP is necessary to maintain the recruited status; (c) the combined effect of opening and keeping open will increase the lung homogeneity, decreasing the likelihood of VILI. Actually, setting the mechanical ventilation within the generally accepted limit of 30 cmH_2O plateau pressure and approximately 15 cmH_2O PEEP associated with protective tidal volume does not satisfy any of the theoretical prerequisites of the open lung strategy ("opening and keeping open") nor its expected advantages (decrease of lung inhomogeneities).

Opening the lung

Opening collapsed lung tissue requires pressures adequate to overcome the sum of defined counterforces: (a) compressive forces due to the increased lung weight [28]; (b) the surface tension forces due to the moving of air/liquid interface from the small airway to the alveolar space [29]; (c) the pressure needed to lift up the chest wall [30]. It is worth reminding that the opening pressures are an "intensive" property of the system, i.e., the same opening pressure is needed in mild, moderate, and severe ARDS to open a given collapsed unit with defined characteristics (compression, surface tension, chest wall

Table 2 Uninflated tissue and intratidal collapse/reinflation at 5 and 15 cmH_2O PEEP

ARDS severity	ECMO	Number of patients	Uninflated tissue grams of tissue (% of lung weight)		*p* value
			PEEP 5 cmH_2O	PEEP 15 cmH_2O	
Mild	–	5	572 ± 99 (46 ± 4%)	516 ± 135 (40 ± 7%)	0.07
Moderate	–	10	608 ± 271 (40 ± 16%)	492 ± 242 (32 ± 15%)	<0.001
Severe	No	9	1029 ± 277 (58 ± 9%)	793 ± 241 (45 ± 10%)	<0.01
	Yes	9	1624 ± 785 (70 ± 11%)	1393 ± 857 (57 ± 16%)	<0.01
ARDS severity	**ECMO**	**Number of patients**	**Collapse/reinflation grams of tissue (% of lung weight)**		***p* value**
			PEEP 5 cmH_2O	**PEEP 15 cmH_2O**	
Mild	–	5	63 ± 26 (5 ± 2.1%)	39 ± 32 (3.2 ± 2.6%)	0.23
Moderate	–	10	92 ± 53 (6.2 ± 3.6%)	78 ± 142 (5.3 ± 9.6%)	0.76
Severe	No	9	110 ± 91 (6 ± 5%)	89 ± 93 (5 ± 5%)	0.57
	Yes	9	135 ± 100 (7 ± 5%)	104 ± 80 (5 ± 4%)	0.32

Upper part of the table summarizes the grams of uninflated tissue measured at PEEP 5 and 15 cmH_2O end-expiration. Lower part summarizes the grams of lung tissue undergoing intratidal collapse and reinflation at PEEP 5 cmH_2O and PEEP 15 cmH_2O at constant tidal volume (i.e., the grams of lung tissue collapsed at PEEP and recruited at the respective plateau pressure). Data were compared with paired *t* test

Table 3 Lung inhomogeneities

	ECMO	PEEP 5 cmH_2O	Plateau 19 cmH_2O	Plateau 28 cmH_2O	Plateau 40 cmH_2O	PEEP 15 cmH_2O	Plateau 27 cmH_2O
Mild ($n = 5$)		17 ± 3	14 ± 1	14 ± 1	14 ± 1	14 ± 2[b]	13 ± 1
Moderate ($n = 10$)		21 ± 6	18 ± 5	16 ± 6[a]	15 ± 7[a]	17 ± 6[b]	15 ± 6
Severe ($n = 18$)	No ($n = 9$)	19 ± 4	18 ± 4	18 ± 5	18 ± 7	19 ± 5	18 ± 5
	Yes ($n = 9$)	16 ± 4	18 ± 4	20 ± 6[a]	20 ± 7[a]	17 ± 4	18 ± 6

The table summarizes the lung inhomogeneities data (% of lung volume) obtained from the 6 CT scans performed during the study in patients with mild, moderate, and severe ARDS. CT scans performed at 5, 19, 28, and 40 cmH_2O were compared with a mixed model ($p = 0.16$ for airway pressure, $p = 0.51$ for ARDS severity, and $p < 0.001$ for interaction). Lung inhomogeneities at the different pressure levels were compared with the lung inhomogeneities at PEEP 5 cmH_2O (12 pre-planned multiple comparisons) and *p* values were corrected with the Benjamini, Hochberg, and Yekutieli method. Lung inhomogeneities at PEEP 5 end-expiration and PEEP 15 end-expiration were compared with paired *t* tests

[a] $p < 0.05$ vs end-expiration PEEP 5 cmH_2O

[b] $p < 0.05$ vs PEEP 5 cmH_2O in the same class of ARDS severity

elastance). The amount of recruitable tissue, instead, is an "extensive" property of the system and, as such, it is proportional to the lung size, to the severity of the disease, and to the distribution of lung edema [30].

The compressive forces cannot exceed the lung height and they generally range between 10 and 15 cmH_2O [28, 31]. The pressures needed to overcome the surface forces in ARDS are estimated in the order of 15–20 cmH_2O [29]. The pressures needed to lift up the chest wall, depending on chest wall elastance, are in the order of 5–10 cmH_2O [30]. Therefore, in ARDS patients, the opening pressures must overcome the sum of compressive, surface, and chest wall forces and, consequently, they range between 30 and 45 cmH_2O. The use of higher airway opening pressures (up to 60 cmH_2O) may result, in some patients, in a negligible additional recruitment, with the risk of possible severe hypercapnia, acidosis, and the need for hemodynamic support [32]. Present data confirm that at set

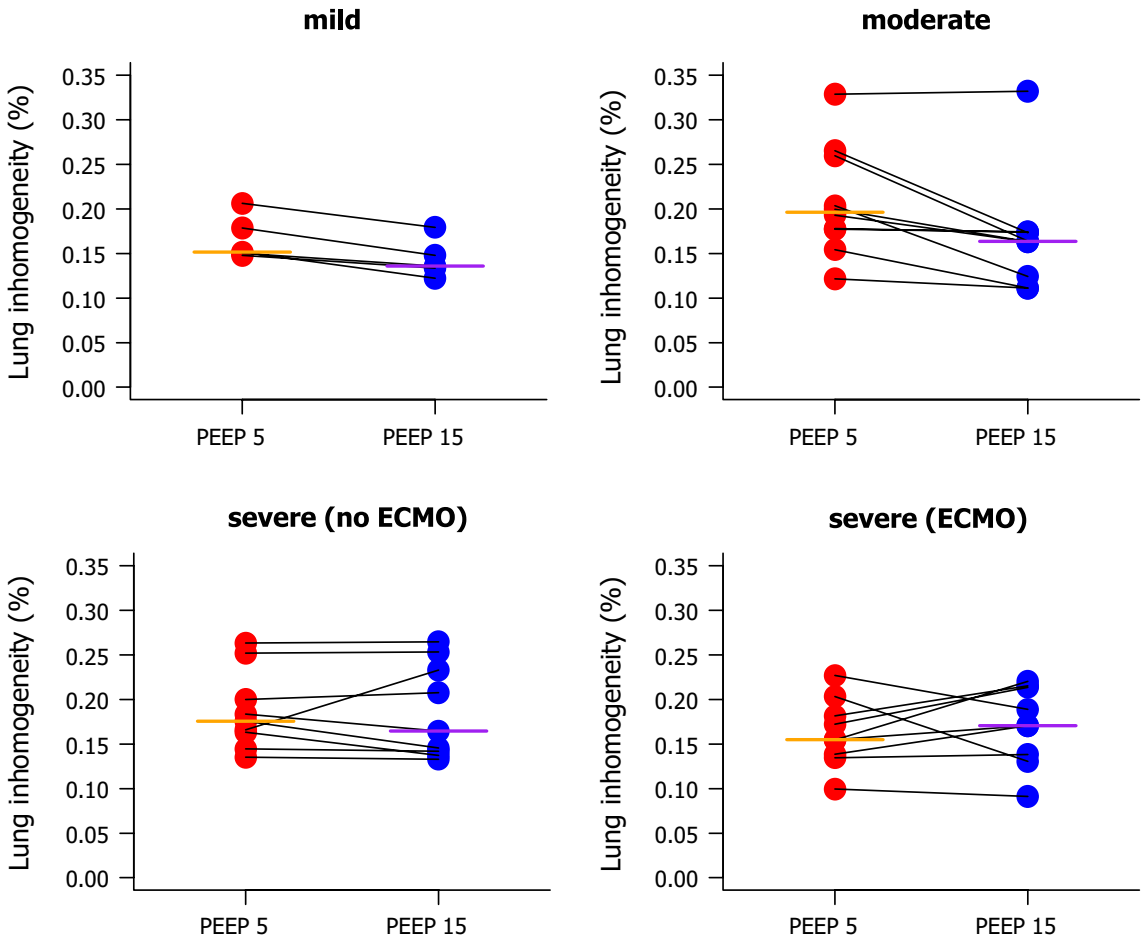

Fig. 3 Lung inhomogeneities and PEEP. The extent of lung inhomogeneity of the individual patients with mild (*upper left panel*), moderate (*upper right*), severe without ECMO (*lower left*), and severe with ECMO (*lower right*) is reported at PEEP 5 (*red circles*) and 15 cmH_2O (*blue circles*). *Orange* and *purple lines* denote median values for inhomogeneity at PEEP 5 and 15 cmH_2O, respectively

pressure of 45 cmH_2O the amount of recruitment is dramatically different between mild, moderate, and severe ARDS [5]. If the inflation pressures, however, are limited to 30 cmH_2O, a significant proportion of the recruitable lung stays closed throughout the whole respiratory cycle, particularly in moderate and severe ARDS.

Keeping the lung open

The open lung approach implies that the tissue recruited at plateau pressure is kept open during the expiratory phase, otherwise "atelectrauma" will ensue. To keep the lung open, "high enough" PEEP must be provided. Several "higher PEEP" methods have been proposed in randomized trials. Some were based on oxygenation (as applied in the ALVEOLI and LOV trials [17, 18], resulting in average PEEP of 13.2 and 14.6 cmH_2O, respectively); some were based on respiratory mechanics (such as the ExPress trial [19], resulting in average PEEP of 14.6 cmH_2O). Other studies were specifically designed to test the open lung strategy and were based on oxygenation or respiratory mechanics changes observed on the expiratory limb of the *P–V* curve (resulting in average PEEP of 15.8 cmH_2O [33]). The method based on transpulmonary pressure resulted in an average PEEP of 17 cmH_2O [34]. In a study comparing different methods for "higher PEEP" selection (i.e., oxygenation, respiratory mechanics, transpulmonary pressure) in the same patient, the resulting PEEP values were not statistically different and averaged 14.5 cmH_2O [35]. Therefore, the bulk of data suggests that PEEP values of approximately 15 cmH_2O are considered "adequate" to keep the lung open in an "average" ARDS population (obviously not necessarily in the single patients).

In a previous work, where we estimated the uninflated tissue at end-inspiration from the *P–V* curve (instead of measuring it from the CT scans, as in the present

work), we found that the tissue undergoing tidal opening and closing decreased significantly from 141 to 63 g in patients with recruitability higher than the median value of that population (average lung weight approximately 1700 g). In the present population we found that the tissue undergoing tidal opening and closing decreased between 5 and 15 cmH_2O from 123 to 96 g in severe ARDS patients (average lung weight approximately 2000 g). Although both studies showed that increasing PEEP to 15 cmH_2O decreased the opening–closing tissue, this remained, however, still relevant in patients with severe ARDS. Therefore, these levels of PEEP seem inadequate for keeping the lung fully open during low tidal volume ventilation (6–8 ml/kg IBW).

Lung inhomogeneity

The result of the open lung strategy, based on Mead's theory, should be a decrease of lung inhomogeneity with a more even distribution of the energy load into the lung parenchyma. This model of "homogeneity" implies that a collapsed region, when opened and kept open, has the same mechanics and inflation of the neighboring already open regions. This would cancel the "stress raisers" and their devastating consequences on lung integrity. Unfortunately, this view is likely to represent an oversimplification. Indeed, in this study we found that the reduction in inhomogeneities was limited only to few a percentage points in mild, moderate, and severe ARDS (without ECMO), while it did not change, despite consistent recruitment, in severe ARDS. This apparent paradox is explained by the behavior of the poorly aerated tissue, which is a determinant source of inhomogeneity [24]. Indeed, the increased homogeneity due to a better inflation of previously poorly aerated tissue is cancelled out by the recruitment of uninflated tissue into new poorly aerated tissue (inhomogeneous) [36]. The final result is that the homogeneity increases much less than expected from the theoretical models, depending on the balance (after recruitment) between the increase in well-aerated tissue (homogeneous), the behavior of poorly aerated tissue (inhomogeneous), and the decrease in uninflated tissue (homogeneous).

Clinical consequences

We believe that our data may call into question some of the current settings of mechanical ventilation and may cast some doubt on the clinical relevance of the atelectrauma. The lung opening is largely applied in ARDS through the recruitment maneuvers. Our data suggest that setting 45 cmH_2O on the ventilator to recruit the lung is unnecessary in mild ARDS, as at 30 cmH_2O plateau pressure most of the recruitment is already achieved. In contrast, in this range of pressures (30–45 cmH_2O), a relevant amount of tissue may be recruited in moderate and severe ARDS. The fate of this recruited tissue, however, depends on how the ventilator is set after the recruitment maneuver. Limiting the plateau pressure to 30 cmH_2O and the PEEP at 15 cmH_2O will lead to the collapse of the tissue recruited between 30 and 45 cmH_2O. To keep open this fraction of recruitable tissue, two alternatives are possible: either the sigh ventilation [37], with all the problems due to the large tidal volumes, or a PEEP level far greater than the one currently used.

Therefore, one should choose between the following alternatives: either to ventilate between 30 cmH_2O plateau and PEEP 15 cmH_2O, accepting that up to 30% of the lung will remain closed and a fraction of atelectrauma is always present, or to use PEEP levels far higher than the ones commonly applied. The clinical question is whether the atelectrauma is less harmful than the possible volutrauma due to a further increase of PEEP. In our opinion, the available theoretical [11] and experimental data [38] suggest that atelectrauma may be safer than volutrauma, although this should be prospectively evaluated in a trial conducted on patients with high recruitability.

Electronic supplementary material

The online version of this article (doi:10.1007/s00134-017-4754-8) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest

Dr. Cressoni and Dr. Gattinoni hold an Italian patent for determination of lung inhomogeneities (0001409041). On behalf of all authors, the corresponding author states that there are no other conflicts of interest.

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