

# Positive end-expiratory pressure: how to set it at the individual level

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**Abstract:** The positive end-expiratory pressure (PEEP), since its introduction in the treatment of acute respiratory failure, up to the 1980s was uniquely aimed to provide a viable oxygenation. Since the first application, a large debate about the criteria for selecting the PEEP levels arose within the scientific community. Lung mechanics, oxygen transport, venous admixture thresholds were all proposed, leading to PEEP recommendations from 5 up to 25 cmH<sub>2</sub>O. Throughout this period, the main concern was the hemodynamics. This paradigm changed during the 1980s after the wide acceptance of atelectrauma as one of the leading causes of ventilator induced lung injury. Accordingly, the PEEP aim shifted from oxygenation to lung protection. In this framework, the prevention of lung opening and closing became an almost unquestioned dogma. Consequently, as PEEP keeps open the pulmonary units opened during the previous inspiratory phase, new methods were designed to identify the 'optimal' PEEP during the expiratory phase. The open lung approach requires that every collapsed unit potentially openable is opened and maintained open. The methods to assess the recruitment are based on imaging (computed tomography, electric impedance tomography, ultrasound) or mechanically-driven gas exchange modifications. All the latest assume that whatever change in respiratory system compliance is due to changes in lung compliance, which in turn is uniquely function of the recruitment. Comparative studies, however, showed that the only possible approach to measure the amount of collapsed tissue regaining inflation is the CT scan. In fact, all the other methods estimate as recruitment the gas entry in pulmonary units already open at lower PEEP, but increasing their compliance at higher PEEP. Since higher PEEP is usually more indicated (also for oxygenation) when the recruitability is higher, as occurs with increasing severity, a meaningful PEEP selection requires the assessment of recruitment. The Berlin definition may help in this assessment.

**Keywords:** Positive end-expiratory pressure (PEEP); mechanical ventilation; lung recruitment

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## Introduction

Barach and colleagues in 1938 fully described the effects of positive end-expiratory pressure (PEEP) as an adjunct to mechanical ventilation for cardiogenic pulmonary edema, sepsis or asphyxia, in experimental animals and in seven

patients with cardiac failure (1). Cournand and colleagues in 1946 measured the dismal effect on hemodynamics caused by the intermittent intrathoracic positive pressure (2). As logical consequence, PEEP was not implemented in clinical practice until the late 1960s, in order to avoid further

impact on the hemodynamic.

In that period, Gregory and colleagues in San Francisco applied PEEP in spontaneous breathing neonates with respiratory distress due to surfactant deficit, without reporting major hemodynamic problems (3). In the same period was described the adult respiratory distress syndrome which, in analogy with the infants' respiratory distress syndrome, was thought to be primarily due to surfactant deficit (4). The adult respiratory distress syndrome, later called acute respiratory distress syndrome (ARDS), became the prototype pathology accompanying the development of intensive care medicine (5) and PEEP was one of the most widely used therapeutic approaches. The first studies on mechanisms of PEEP during ARDS were performed by Falke and colleagues at the Massachusetts General Hospital (6), while the most popular clinical approach for PEEP setting was proposed by Suter as a function of oxygen transport and respiratory mechanics (7). In the meantime, Kirby and colleagues, from Miami, proposed the use of a "super PEEP", that is PEEP up to 25 cmH<sub>2</sub>O, somehow forerunner of the "open lung approach" (8). Tenaillon, from the French side, proposed to increase PEEP up to whatever level was sufficient to decrease the venous admixture below 10% (9). Dantzker, revisiting the Cournand worries, claimed that the primary mechanism of PEEP in improving oxygenation was through a decrease of cardiac output (10). Indeed, venous admixture and cardiac output are linearly related, as firstly described by Lemaire *et al.* in that same period (11,12). It is interesting to note that, within the variety of approaches proposed, tested and discussed, two points were unquestioned: first, the use of PEEP was uniquely linked to the oxygenation; second, the hemodynamic effects were always taken into account.

A major breakthrough in the history of PEEP was the discovery that the inflammatory reaction, as measured by cytokines analysis, was prevented/dampened by the use of PEEP (13). Mead's theoretical model provided the foundations for the atelectrauma theory (14), which was then illustrated by Lachmann (15) and clinically corroborated by Ranieri (16). Since the 90s, following a series of experimental observations that found PEEP effective in preventing huge lung edema, beginning with the Webb and Tierney findings (17), PEEP was not considered anymore a mere means to improve oxygenation, but a tool to protect the lung. The emphasis on lung protection led to a progressive oblivion of the PEEP-related hemodynamic complications, and only a few centers continued through the years to report and underline the crucial role of

hemodynamics in the framework of PEEP (18-20).

In this paper, we would like to discuss the use of PEEP from these two different perspectives (oxygenation and lung protection) and to speculate on its 'personalized' application.

## Mechanisms of PEEP

To properly apply PEEP, it is first mandatory to understand how it works, its benefits and its drawbacks. PEEP is usually related to lung recruitment and it is common to read statements as "PEEP-related recruitment". This is misleading for at least four reasons:

- (I) PEEP is an intensive property of the system, while the recruitment is a capacitive property;
- (II) Recruitment is an inspiratory phenomenon, while PEEP relates to the expiratory phase;
- (III) PEEP, through transpulmonary pressure acts not only on recruitable pulmonary units, but on every pulmonary units open to the ventilation;
- (IV) PEEP acts not as such, but through the transpulmonary pressure.

### Intensive and capacitive properties

By definition, an intensive property of a system is a physical property whose magnitude is independent of the size of the system, while a capacitive (or extensive) property strictly depends on the size system. In other words, a pressure (such as a PEEP) of 10 cmH<sub>2</sub>O is the same, either applied to the lung of a mouse or to the lung of an elephant. On the contrary, the same percentage of recruited tissue means an enormous difference in absolute value, as recruitment is a capacitive property. This distinction is not just academic, as we will discuss later.

### Inspiratory and expiratory recruitment

#### Inspiratory recruitment

During inspiration, if the applied pressure is sufficient, previously collapsed pulmonary units will open and inflate. We have then to understand: first, why and how the units are collapsed; second, where are they located; finally, how the opening pressures actually work.

- (I) A collapsed unit may be defined as a pulmonary unit where the gas content is near zero or nil. The first kind of collapse [loose atelectasis (21)] is due to the small airways collapse, primarily because of

the increased lung weight; this “squeezes” the gas out of the unit and closes the small airways. Some gas is left behind the collapsed airway (gas content near zero). The second kind of collapse [sticky atelectasis (21)] is due to the complete reabsorption of the gases from the pulmonary unit. This occurs whenever and wherever a tributary airway stays closed throughout the entire respiratory cycle. During ARDS, other pulmonary units may present as a gasless, but are “consolidated” instead of collapsed. These units are usually filled with liquid/solid material originating from the disease process leading to ARDS. In practice, collapsed and consolidated units may be differentiated only after a given “maximal” opening pressure is applied;

- (II) The number of units in which the collapse is primarily due to the gravitational forces increases when the superimposed pressure (i.e., the lung mass times the vertical height) increases (22–24). It must be noted, however, that the units at a given iso-gravitational plane aren’t necessarily all open or all closed, as local phenomena of interaction between contiguous units may prevent or favor their closure. Note that the unit collapsing at end-expiration remains “loose” if they reopen and receive gas during the next inspiration, otherwise they become “sticky” atelectasis with time. While the most frequent loose atelectasis follows a quite definite spatial orientation (from non-dependent to dependent lung) (25,26), the reabsorption atelectasis arises both in the most dependent lung regions (where the inspiratory pressure isn’t sufficient to open the gravitational dependent collapsed units) and wherever an airway obstruction occurs for non-gravitational reasons;
- (III) To open a given unit the applied pressure must overcome at least four distinct forces (ignoring the gas movement):
  - (i) The surface tension forces (27). These are likely lower in the “loose” atelectasis, where some gas is still present, than in the “sticky” atelectasis, where all the water molecules are in contact with each other;
  - (ii) The pressure superimposed to that given unit (22,23);
  - (iii) The pressure likely due to the interaction between neighboring units collapsed in an iso-gravitational plane (28);

- (iv) The pressure needed to lift up the chest wall at the same volume to which the lung has been inflated (24).

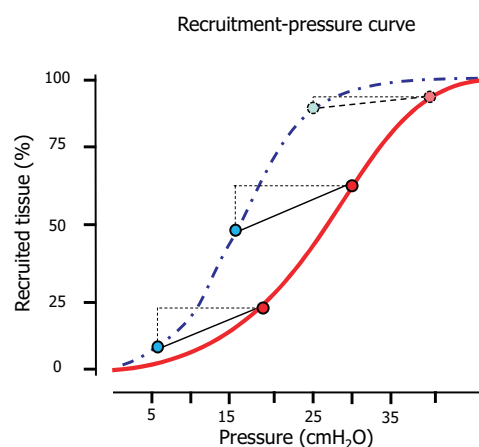
Taking into account all these phenomena may contribute in understanding the behavior of the opening pressures. In *Figure 1* we present an inspiratory recruitment-airway pressure curve measured in 34 ARDS patients. As shown, the shape is sigmoidal (29,30), which, expressed as opening pressure distribution, results in a Gaussian curve. Accordingly, most of the recruitment occurs at 20 cmH<sub>2</sub>O, while few units require either very low pressures or very high pressures (26,31). Actually, considering a standard sternum-vertebral height of 15 cm, a normal chest wall elastance and the pressure required to overcome the tension forces, ignoring the interaction between neighboring units, the order of magnitude for opening a unit compressed by 15 cmH<sub>2</sub>O (a theoretical limit) would be:

$$\text{Opening pressure} = \text{compressive forces (10–15 cmH}_2\text{O)} + \text{surface tension (15–20 cmH}_2\text{O)} + \text{chest wall (5–10 cmH}_2\text{O)} = 30\text{–}45 \text{ cmH}_2\text{O}$$

As shown, at 45 cmH<sub>2</sub>O, most of the possible recruitment should be accomplished in the majority of the patients. A minor fraction (2–3%) of the recruitment may occur at higher pressure (45–60 cmH<sub>2</sub>O) (31), possibly due to the interaction between collapsed units. Therefore, to open completely the lung, pressures as high as 45 cmH<sub>2</sub>O (if the thoracic cage is normal) are usually required. Of note, at the recommended plateau pressure of 30 cmH<sub>2</sub>O (32), a consistent fraction of the lung (up to 30% in severe ARDS) remains closed (28).

### Expiratory recruitment

It is well known that the pressures needed to keep open a given pulmonary unit are far lower than the ones required for opening it. The main reason is that the fraction of pressure which was required to overcome the surface forces during inspiration is no longer necessary during expiration. Actually, the surfactant function was identified by analyzing the differences between a lung volume-pressure curve performed inflating the lung with gas (surface forces present) or with saline (surface forces absent) (33,34). As a result, the pressure needed to keep the lung open is far lower than the one needed for opening it (see *Figure 1*). As shown, most of the lung is kept open at airway pressure around 10 cmH<sub>2</sub>O. Pressures as high as 20–25 cmH<sub>2</sub>O may be necessary to keep open some pulmonary units.



**Figure 1** The diagram shows a possible pressure-recruitment curve. The values have been taken from Cressoni *et al.* (28). The point on the inspiratory limb (solid red line) at pressure of ~30 cmH<sub>2</sub>O and at ~18 cmH<sub>2</sub>O represents the average inspiratory recruitment starting from 15 and 5 cmH<sub>2</sub>O PEEP respectively. The two points at ~15 and ~5 cmH<sub>2</sub>O along the expiratory limb (dotted black line) represent the recruitment measured at those levels of PEEP. As shown, the amount of tissue undergoing recruitment and derecruitment between end-inspiratory and end-expiratory points is similar at 5 and 15 cmH<sub>2</sub>O PEEP. The tidal volume was the same at the two PEEP levels. The upper two points are hypothetical. See text for details. PEEP, positive end-expiratory pressure.

### Recruitment versus inflation

Anytime the end-expiratory pressure is applied, it will keep open a certain fraction of the previously recruited lung, while keeping the already opened lung units at a higher level of inflation. If we define, as we believe correct, the recruitment as the mass of pulmonary units regaining and maintaining inflation, it is convenient to estimate how much of the gas volume due to the presence of PEEP is distributed in the newly recruited units and how much is distributed in already open units. As shown in Figure 2, most of the PEEP volume enters the units already inflated (35). Therefore, the effect of PEEP is dual: on one side, it maintains a minimal amount of gas in newly opened units; on the other side, it increases the aeration of the units already open, even causing an overstretch. In Figure 3 we present a model of distribution for a PEEP increase from 0 to 25 cmH<sub>2</sub>O in a hypothetical representative ARDS lung. It must be noted that in most of the cases, a pressure of 20 cmH<sub>2</sub>O generates an end-expiratory lung volume (EELV)

almost equal to the total lung capacity (TLC). This is the volume on which the tidal volume ( $V_T$ ) is superimposed. The recruitment of new tissue and expansion of previously inflated lung accounts for the large difference reported in literature where recruitment is assessed (35). The CT scan allows to exactly quantify the amount of lung tissue regaining by inflation. The magnitude of this fraction, related to the total lung weight, ranges between 0 and 40% with a median value around 10–12%, depending on the severity of the studied ARDS population. In contrast, all the recruitment assessment based on gas measurements, such as the dual volume-pressure curve method or the gas method we implemented in 1998 (37) and Dellamonica reintroduced in 2011 (38), do not measure only the gas entering in the previously degassed regions, but also the amount of gas entering the already open units, which, at higher volume, increase their compliance (35).

### Transpulmonary pressure

It must be noted that all the above considerations should refer not to the airway pressure, but instead to the transpulmonary pressure. In a given patient, changes in transpulmonary pressure are related to the changes of airway pressure by the following relationship (39):

$$\text{Transpulmonary pressure } (P_L) = P_{aw} \times E_L / E_{tot}$$

Where  $P_{aw}$  stands for airway pressure,  $E_L$  elastance of the lung and  $E_{tot}$  elastance of the respiratory system (i.e., elastance of the lung plus elastance of the chest wall).

It must be noted that the so-called transmission is related to the ratio of the lung to the total elastance. This, in normal conditions, is ~0.5, while in ARDS it can range between 0.2 and 0.8. This underlines the need for measuring the transpulmonary pressure for a safer application of mechanical ventilation.

### Clinical application of PEEP

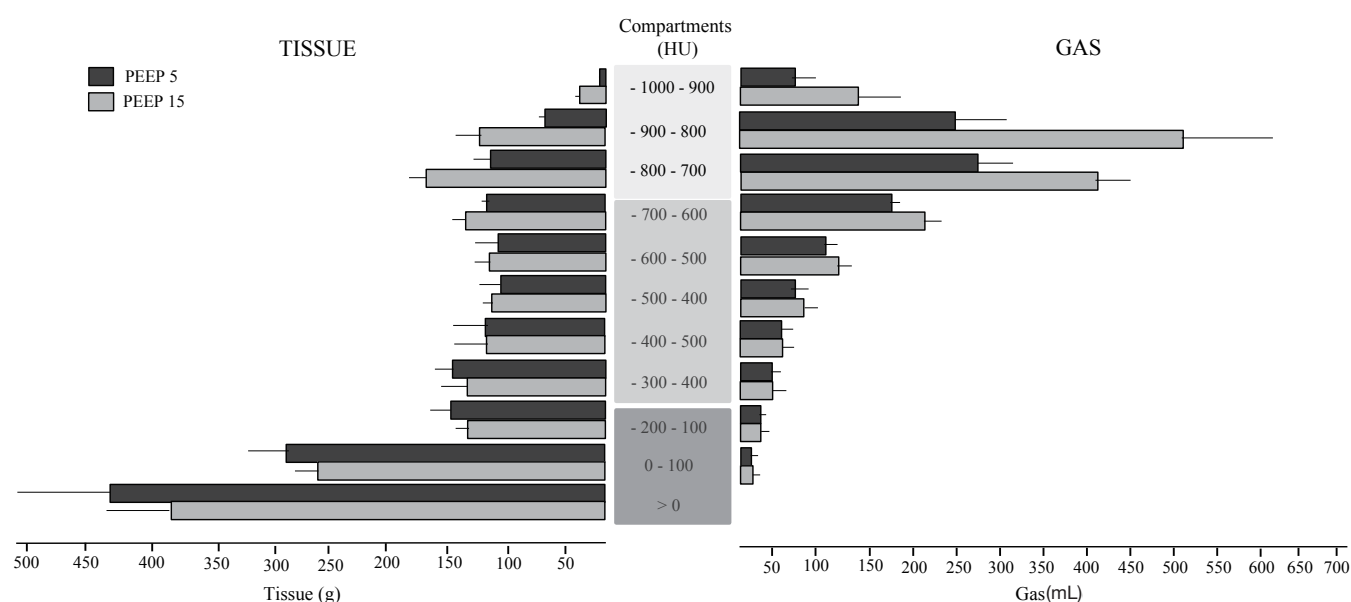
#### PEEP targets

When selecting the PEEP level, we should consider the oxygenation advantage and the putative benefits on “lung protection”.

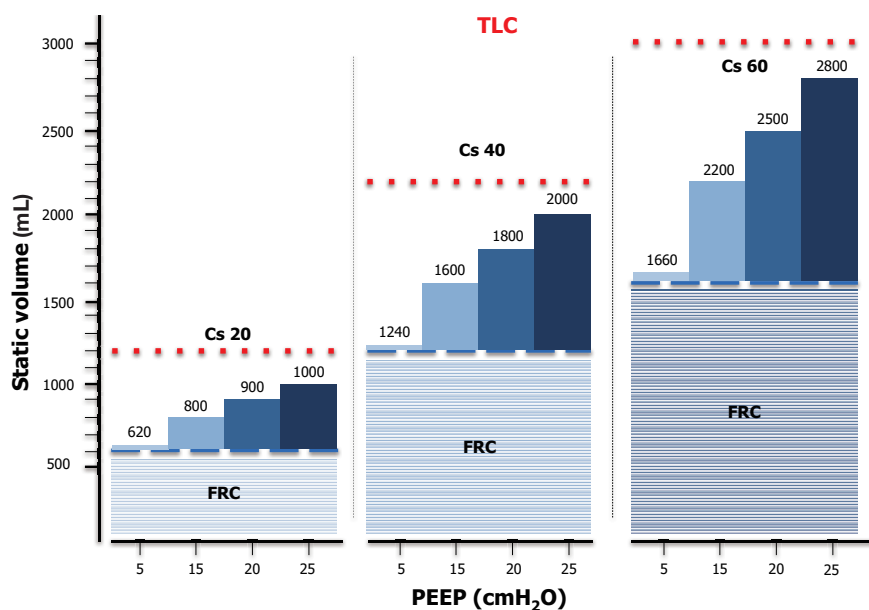
#### PEEP and oxygenation

For decades, the sole purpose of introducing PEEP in the





**Figure 2** Redrawn from Chiumello and colleagues (35). The figure presents the different gas-tissue distribution at 5 and 15 cmH<sub>2</sub>O PEEP (dark and light grey, respectively). As shown, the non-aerated tissue regaining aeration is minimal, while most of the inflation goes to already open units (normally aerated tissue). This distribution is the basis for the difference observed between CT-scan methods and all the gas-based methods in assessing recruitment. PEEP, positive end-expiratory pressure.



**Figure 3** As representative values we assumed FRCs of 600, 1,200 and 1,600 mL and static compliances of the respiratory system of 20, 40 and 60 mL/cmH<sub>2</sub>O for severe, moderate and mild ARDS respectively. At each PEEP level (5, 15, 20 and 25 cmH<sub>2</sub>O), the volume due to PEEP was computed as compliance multiplied by PEEP. As shown, the total height of each bar (i.e., FRC plus PEEP volume) represents the starting point to which the tidal volume is added. This underlines how, when tidal volume is added to PEEP volume, it becomes extremely easy to overcome the TLC limits, at which the extracellular matrix is at risk of micro-fractures or rupture. See also Protti *et al.* (36). PEEP, positive end-expiratory pressure; ARDS, acute respiratory distress syndrome; TLC, total lung capacity.

ARDS management was to improve oxygenation. Less attention was paid to the  $\text{PCO}_2$ , and its possible protective effects were not really considered, although proposed in experimental animals, until the development of the “atelectrauma theory” in the late 1980s. PEEP improves oxygenation through two possible mechanisms: (I) keeping open previously collapsed and perfused regions, causes an intra-pulmonary right-to-left shunt (venous admixture) decrease; (II) decreasing the cardiac output, generates a reduction of intra-pulmonary right-to-left shunt.

- ❖ Although low ventilation-perfusion (VA/Q) regions are represented in ARDS, the main mechanism of hypoxemia is the relevant presence of right-to-left shunt (40). Indeed Riley’s model (41), referring to the lung as a three-compartment reality (dead space, “normal VA/Q” and shunt) well applies to the ARDS lung. The shunt fraction is usually lower than the fraction of non-aerated tissue due to hypoxic vasoconstriction, which is dampened, but still present (42). If PEEP is able to maintain open units previously collapsed and perfused, the shunt fraction decreases.
- ❖ ARDS is characterized by elevated vascular resistance due to diffuse vasoconstriction. The vessels serving open pulmonary units, however, are more dilated than the ones serving collapsed units. An increase of cardiac output, associated with an increase of pulmonary artery pressure is preferentially distributed in these latter units, increasing the right-to-left shunt (11,12). While these mechanisms are likely operating when PEEP is present, they have been challenged during unsupported spontaneous breathing (43).

Due to these dual mechanism, PEEP and more in general the increase of pressures, is associated in nearly the totality of cases, with an increase in  $\text{PaO}_2$ . A decrease of  $\text{PaO}_2$  when PEEP is increased must be carefully investigated, as it may reveal unusual mechanisms operating in the system (44-46).

If PEEP is used to provide viable oxygenation but with a minimum risk of overinflation and of hemodynamic instability, a reasonable  $\text{PaO}_2$  target should be established. In our opinion, this approach lacks sound physiological background. Referring only to a  $\text{PaO}_2$  value is insufficient, as what matters is the tissue oxygenation (served by hemodynamics), which decreases while the  $\text{PaO}_2$  increases when PEEP is applied. A right balance should be pursued by the physician, taking into account the trajectory of the

disease, the patient’s physiological reserve and the relevance of possible comorbidities.

### PEEP and lung protection

The protective effect of PEEP is commonly referred to a seminal paper by Webb and Tierney, who showed, in 2-hour experiments on rats, that lung edema was worse when ventilating the lungs between 45  $\text{cmH}_2\text{O}$  plateau and 0  $\text{cmH}_2\text{O}$  PEEP than 45  $\text{cmH}_2\text{O}$  plateau and 10  $\text{cmH}_2\text{O}$  PEEP (17). This figure is still today reported in meetings and papers as an unquestionable proof of the protective effect of PEEP. In the same paper, Webb and Tierney also report data (mostly neglected) showing that ventilating at 30  $\text{cmH}_2\text{O}$  plateau and 0  $\text{cmH}_2\text{O}$  PEEP did not cause dramatic damages. Despite the large consensus on the importance of atelectrauma, and its prevention by PEEP, bedrock of the protective lung strategy, in our opinion the role of PEEP should be reappraised. Actually, the basic question is whether the protection of PEEP is just a side effect of the decrease in tidal volume, commonly associated with the increase of PEEP since the Webb and Tierney experiments, or, in contrast, if the PEEP acts directly on preventing barotrauma and VILI, as proposed by the lung protective strategy. We think that considering the PEEP protective is more a belief (47) than an evidence or even a physiology-supported reality. Actually, we doubt the direct protective effect of PEEP (particularly of higher PEEP) for three main reasons:

- (I) PEEP is a pressure and as such it is a component of the mechanical power, which is delivered to the lung parenchyma. To distend a lung, energy must be supplied, higher than the one used to keep it distended, and the pre-stressed fibers may reach their unphysiological limits (48);
- (II) A large series of experiments led to the conclusion that what really matters is the mechanical power overcoming the physiological upper limit of the lung. If this is not reached, the presence of PEEP or its absence is irrelevant. If the PEEP is so high that the associated tidal volume overcomes the physiological limits of lung expansion, PEEP is harmful (36);
- (III) Three large studies comparing, despite different methodological approach, lower PEEP (in the range of 8  $\text{cmH}_2\text{O}$ ) to higher PEEP (in the range of 15  $\text{cmH}_2\text{O}$ ) did not find any significant difference. That means that the putative atelectrauma associated with lower PEEP is not more dangerous

than the putative volutrauma associated with higher PEEP (49).

This does not indicate that PEEP is useless, but simply that the open lung theory is not necessarily a correct conceptual approach.

### PEEP in individual patients

#### Patient characterization

The most important preliminary step in the PEEP selection process, either if the target is exclusively to improve oxygenation either to obtain a fully open lung, is to assess the lung recruitability, an extensive property of the system which solely depends on the nature and the extent of the disease leading to the ARDS (50). Several methods have been suggested to directly, or indirectly, assess lung recruitability, based either on imaging (direct assessment) or on gas exchange/respiratory system mechanic variables during challenge tests (indirect methods).

#### (I) Imaging:

- (i) CT scan. The best tool to measure the recruitability is by quantitatively analyzing two CT scans taken at different pressure levels. The difference between the amount of gasless tissue at lower pressure and the gasless tissue at higher pressure, normalized for lung weight, gives the percent recruitability (51);
- (ii) Electric impedance tomography (EIT). The advantage of using this technique is its availability at the bedside. However, it reflects more a better overall aeration of the lung between two levels of PEEP than the opening of previously gasless tissue. Accordingly, the CT scan-EIT correlation in assessing the recruitability is quite poor (52), while it is better if compared with gas-assessed recruitability (53). It is worth re-emphasizing that the gas method preferentially measures the better inflation at higher PEEP of previously inflated units at lower PEEP than the opening of previously collapsed units (35);
- (iii) Ultrasound. Also this technique is available at the bedside (54). Beside the enthusiasm of their early proponents (55), it suffers, in our opinion, from several limitations, as the lack of spatial resolution and the limited penetration of ultrasound. Finally, as the EIT and the gas-based methods, it is related with the overall

better inflation instead of the opening of previously non aerated tissue;

#### (II) Challenge tests. A complete review of the different tests has been recently published (56) and here we will only summarize them:

- (i) PEEP test during inspiration. Typically, 5, 10 and 15 (sometimes up to 20) cmH<sub>2</sub>O are applied, 15 to 30 minutes apart (equilibration time may be reduced to 10 minutes) (57);
- (ii) PEEP test during expiration. After a full inflation up to 45 cmH<sub>2</sub>O (or sometimes 60 cmH<sub>2</sub>O), airway pressure with PEEP around 25 cmH<sub>2</sub>O, the PEEP is progressively decreased until either oxygenation or respiratory system compliance deteriorates. This value is considered as the beginning of lung collapse (58,59);
- (iii) Another possibility is to use the Berlin classification when PaO<sub>2</sub>/FiO<sub>2</sub> ratio is assessed at 5 cmH<sub>2</sub>O PEEP. In this case, we may expect, with some degree of probability (70–80%), that recruitability reflects the ARDS severity (60).

Each of these systems presents its own problems. The CT scan requires an intense work, both for the test and the analysis. The EIT is promising, but at the moment it is semi-quantitative. The ultrasound can only explore the “shell” of the lung. All the tests referring to the gas exchange variables do not take into account the role of the hemodynamics, nor the behavior of PaCO<sub>2</sub>. An increase of PaCO<sub>2</sub> at constant minute ventilation usually indicates an increase of overinflation (i.e., pulmonary units more inflated and less ventilated). As a surrogate for hemodynamics, it can be useful to consider the central venous hemoglobin oxygen saturation (ScvO<sub>2</sub>). If both arterial oxygenation and ScvO<sub>2</sub> increase, it is likely that hemodynamics are well preserved. Attention should be paid when the oxygenation increases and the saturation does not, since possible danger for the hemodynamics may be displayed by an increase of PaO<sub>2</sub> associated with a decrease of central venous saturation. Therefore, the assessment of the arterial-venous oxygen content difference may prevent us to wrongly attribute to recruitment an increase of PaO<sub>2</sub> simply due to a cardiac output decrease (61).

#### Choice of PEEP

Once the recruitment has been assessed, we have to balance the possible benefits and risks of different levels of PEEP. When different PEEP selection methods were compared,

the one based on the revised P/F ratio-PEEP table, which is based on experts opinion (62), was the only one which provided lower PEEP in patients with lower recruitability, compared to methods based on lung mechanics (63,64), transpulmonary pressure (65), or CT scan (24). Most of the lung mechanics-based methods, and even the CT-based method, did provide equally higher PEEP in patients with high, intermediate or low recruitability as inferred from a modified Berlin classification (49). By the way, we recently showed that a lung cannot be fully opened at ventilation set between 15 cmH<sub>2</sub>O PEEP and 30 cmH<sub>2</sub>O plateau pressure (28). The full opening likely requires PEEP greater than 25 cmH<sub>2</sub>O, whatever the recruitability is. Indeed, to keep open 1 or 1,000 grams of non-aerated tissue (extensive property) requires the same PEEP if the opening pressures are the same. In addition, in routine practice, the PEEP used worldwide in severe ARDS lies around 8.5 cmH<sub>2</sub>O, suggesting that in the normal clinical practice the intensivist targets more a viable oxygenation than an open lung (66). Therefore, it is quite clear that nobody has the recipe for some ideal PEEP setting that likely doesn't exist. We believe that in early full-blown ARDS the severity and the recruitability suggest that values around 15 cmH<sub>2</sub>O in severe patients, although non preventing the opening-closing, are sufficient to keep open at least 70% of the lung and to provide viable gas exchange. In moderate ARDS, values around 10 cmH<sub>2</sub>O are indicated and in mild ARDS even lower PEEP is more than adequate, since the recruitability is extremely low (67).

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## Footnote

**Conflicts of Interest:** The authors have no conflicts of interest to declare.

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