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Inflection point, positive end-expiratory pressure, and alveolar recruitment in acute respiratory distress syndrome

Inflektionspunkt, positiver end-expiratorischer Druck, und alveoläres Rekruitment beim akuten Atemnotsyndrom

Zusammenfassung Eine Störung der arteriellen Oxygenation wegen eines echten intrapulmonalen Shunts ist ein Hauptmerkmal des akuten Atemnotsyndroms (ARDS). Eine Verbesserung der arteriellen Oxygenation bei Patienten mit ARDS kann nur erreicht werden, indem die früher geschlossenen Lufträume wieder eröffnet werden, wobei die Anwendung von PEEP seit längerer Zeit als Methode der Wahl gilt. Daher sind die Verhältnisse zwischen PEEP und dem alveolären Rekruitment von großer klinischer Bedeutung.

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Das alveoläre Rekruitment kann indirekt ausgewertet werden durch die Aufzeichnung verschiedener Parameter wie: die Shuntfraktion, der alveoläre Totenraum, die funktionelle Restkapazität (FRC), die Form der dynamischen Druck-Volumen-Kurve (P-V), und die Steilheit der statischen P-V-Kurve.

Die letztere Methode, in welcher ein unterer Inflektionspunkt innerhalb der Atemwegs-P-V Kurve (P-V,rs) identifiziert wird, stellt eine der häufigst angewendeten Methoden sowohl in der klinischen Praxis als auch in der Forschung dar. Das Verhältnis zwischen einem LIP in der P-V,rs-Kurve und dem alveolären Rekruitment wurde jedoch vor Kurzem in Frage gestellt. In der Tat wird ein LIP nicht nur in der P-V Kurve der Lunge, sondern auch in der P-V-Kurve der Brustwand gesehen und es ist gezeigt worden, daß bei einigen Patienten das in der P-V,rs gesehene LIP nur der Brustwand und nicht der Lunge zuzuschreiben ist.

Eine quantitative Schätzung des alveolären Rekruitments kann durch eine Analyse der bei verschiedenen PEEP-Ebenen gezeichneten P-V-Kurven erfolgen, oder durch eine CT-Scan-Auswertung der Veränderungen der Gasverteilung innerhalb der Lunge. Studien, welche mit diesen Methoden durchgeführt wurden, deckten ein schwaches Verhältnis zwischen dem unteren Inflektionspunkt der P-V,rs-Kurve und dem alveolären Rekruitment auf. Es wurde gezeigt, daß das Rekruitment sich fortsetzt, selbst wenn PEEP nach dem LIP eingestellt wird. Diese Befunde haben direkte klinische Bedeutung, weil eine ventilatorische Strategie, welche die Optimierung des alveolären Rekruitments zum Ziel hat, muß, zumindest in den frühen Stadien der Krankheit, einen ausreichend hohen Atemwegsdruck garantieren, um sämtliche kollabierenden Kräften zu überwinden.

Schlüsselwörter Akutes Atemnotsyndrom – respiratorische Mechanismen – mechanische Beatmung – alveoläres Rekruitment

Summary Impaired arterial oxygenation due to a true intrapulmonary shunting is a key feature of the acute respiratory distress syndrome (ARDS), and every effort should be made to improve oxygen delivery to the body's tissues. In patients with ARDS an improvement in the arterial oxygenation can be obtained only by reopening previously closed airspaces, and the application of PEEP has been recognized, for a long time, as the method of choice to reach this goal. Therefore, the relationships between PEEP and alveolar recruitment are an issue of great clinical interest.

Alveolar recruitment can be evaluated indirectly by recording the changes of several parameters, such as, the shunt fraction, the alveolar dead space, the functional residual ca-

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pacity (FRC), the shape of the dynamic pressure-volume (P-V) curve, and the slope of the static P-V curve.

This latter method, which consists of finding a lower inflection point on the total respiratory system P-V curve (P-V,rs), is one of the most employed methods in both the clinical practice and the research field. However, the relationship between a LIP on the P-V,rs curve and alveolar recruitment have recently been questioned. In fact a LIP can be found not only on the lung P-V curve, but also on the chest-wall P-V curve, and it has been shown that in some patients, the LIP seen on the P-V,rs is due to the chest-wall only and not to the lung.

A quantitative estimation of the alveolar recruitment can be done by the analysis of the P-V curves drawn at different levels of PEEP, or by the a CT scan evaluation of the changes in gas distribution within the lung. Studies done with these methods have led to a demonstration of a weak relationship between the lower inflection point on the P-V,rs curve and the alveolar recruitment. In fact, it has been shown that a recruitment continues to occur even when PEEP is set beyond the LIP. These findings have a direct clinical implication in that a ventilatory strategy aimed at optimization of the alveolar recruitment must guarantee, at least in the early phase of the disease, an airway pressure high enough to overcome all the collapsing forces.

Key words Acute respiratory distress syndrome – respiratory mechanics – mechanical ventilation – alveolar recruitment

Introduction

Impaired arterial oxygenation, due to a true intrapulmonary shunting, is a key feature of the acute respiratory distress syndrome (ARDS) [4]. A true intrapulmonary shunting is possible only when blood flows through non-ventilated alveoli and three different mechanisms can be taken into account to explain this finding:

1) the filling of airspaces by exudate, cellular debris, pseudomembranes, and inflammatory cells as a consequence of the structural damage of the alveolar-capillary unit [61];
2) the collapse of the terminal airway as a consequence of the reduction in lung volume and a damage or loss of the lining surfactant [52];
3) atelectasis due to a compression mechanism because of the increased weight of the overlying edematous lung parenchyma [26] or because of a reabsorption mechanism due to the high O_2 concentration in the inspired gas [13].

Since the perfusion of the non-ventilated alveoli is preserved, increasing O_2 concentration in the inspired gas is ineffective in improving PaO_2 (refractory hypoxemia) and the only way to oxygenate the patient is to reduce true shunt fraction by reopening closed airspaces. The improvement of the oxygenation may be potentiated by the inhalation of nitric oxide [53] which diffuses across the alveolar barrier and causes a relaxation of the vascular smooth muscle with a reduction in the pulmonary arterial pressure and an improvement of the ventilation perfusion ratio because a higher proportion of the blood flow redistributes to the ventilating lung units [56].

Artificial ventilation with positive end-expiratory pressure (PEEP) has been long recognized [3] as the treatment of choice to reopen closed airspaces. In this perspective, the ventilatory adjustment should be aimed at the optimization of the alveolar recruitment without interfering with the structure and the function of the lung. Unfortunately, this is not an easy task: first, because the lung damage is not homogeneously distributed and consolidated zones coexist with normally aerated zones [23] which, under the effect of PEEP, can be overinflated [27] and damaged [17]; second, because alveolar recruitment is usually not evaluated in the clinical setting and, therefore, the relationships between PEEP and recruitment are in general inferred from indirect measurements.

Evaluation of the alveolar recruitment

Alveolar recruitment may be investigated by several direct or indirect methods.

Gas exchange

One possible approach is to consider the changes in arterial PO_2 which follow the changes in the level of PEEP, assuming that an increase in oxygenation reflects an increase in the number of functioning lung units. However, PEEP reduces the cardiac output and, therefore, the perfusion of the unventilated lung is also reduced [14, 15]. The complex interplay between the intrapulmonary and the extrapulmonary determinants of the gas exchange caused by PEEP make this method unsuitable to evaluate the effects of PEEP on the true alveolar recruitment.

Functional residual capacity (FRC)

The effects of PEEP on end-expiratory lung volume could apparently be a good choice. As a matter of fact it has been demonstrated that in patients with ARF, the FRC is reduced and the oygenation correlates with resting lung volume [32]. However, the measurement of FRC can not discrim-

inate between the true alveolar recruitment and the increase in the volume of previously expanded alveoli. Recent work has demonstrated that these two distinct phenomena are simultaneously present in patients with ARF under PEEP treatment [8, 28] and, therefore, the measurement of the FRC can not be considered a valid method to evaluate true alveolar recruitment.

Alveolar dead space

At constant tidal volume, the recruitment of collapsed alveoli results in a greater portion of VT being distributed to the functioning alveolar units, so that the functional dead space and arterial to end-tidal CO_2 gradient are reduced. Incremental application of PEEP should be followed by a reduction of alveolar dead space until overexpansion prevails on the alveolar recruitment; at that point dead space again begin to increase [6, 10, 48].

Changes of the respiratory system compliance

In 1975, Suter [58] demonstrated that application of increasing levels of PEEP in patients with ARDS resulted in an initial increase in compliance of the total respiratory system which reached a maximum and then decreased. This trend paralleled the changes in oxygen transport and in dead space ventilation, suggesting that maximal alveolar recruitment was reached, followed by lung overdistension if PEEP was further increased.

Static pressure-volume curve of the total respiratory system (P-V,rs curve)

In patients with ARDS, an inflection zone is often observed in the initial portion of the static P-V,rs curve [33]. The improvement of P-V relationship with increasing pressure is believed to be due to a progressive recruitment that is completely achieved once the curve becomes linear [42].

Shape of pressure curve during constant flow ventilation

Ranieri and coworkers [55] found that the shape of the dynamic P-V curve with zero end-expiratory pressure (ZEEP) was able to predict the effects of PEEP on alveolar recruitment, as judged by static P-V curve and gas exchange. In fact, the patients who exhibited a convex (toward the volume axis) shape and in whom compliance decreased with inflation volume did not show an alveolar recruitment with PEEP, whereas the patients who exhibited a concave shape, the application of PEEP resulted in an alveolar recruitment. This method offers the possibility of monitoring effects of PEEP on alveolar recruitment simply by observing the shape of P-time profile that, during constant flow ventilation, is identical to the V-P curve profile (the time axis, during constant flow ventilation, can be taken as the volume axis in the V-P curve).

CT scan imaging

Recently CT has been used to study alveolar recruitment. Gattinoni and coworkers [22–28] studied the effect of PEEP on alveolar recruitment by a quantitative analysis of the CT scan based on the gas-tissue ratio distribution along the lung and were able to differentiate between the true recruitment and hyperinflation. Puybasset et al. [53] followed an anatomic approach by a visual estimation of the percentage of the aerated lung parenchyma after a systematic marking of all the lung segments. These methods are unique in that they offer the possibility to perform not only a qualitative, but also a quantitative evaluation of the true alveolar recruitment, to distinguish between recruitment and overinflation and to visualize where they occur. On the other hand they are complex, require a specific skill, are expensive, and need patients to be transported to the radiological department.

Among these various methods, the one based on the P-V curve analysis has been considered the more suitable compromise as it offers unquestionable advantages: it is technically simple, it is feasible at the bed side [20], and the data that can be obtained correlate with the clinical stage of the disease [33]. Moreover, a recent work by Amato and colleagues [2] has provided a demonstration that using the P-V curve to set the patterns of mechanical ventilation in order to maximize the recruitment and to avoid hyperdistention can have a real impact on the clinical outcome of the patients with ARDS.

Pressure-volume curve

The P-V curve explores the static mechanical properties of the total respiratory system and/or of its components, that is the lung (L) and the chest wall (w), when they are expanded from resting volume to a final volume usually corresponding to the tidal volume or to the vital capacity and when they are deflated from the final volume again to the resting volume.

Two methods are available to build up the P-V curve in curarized intubated patients: 1) the step-by-step method, where the chest is inflated and deflated stepwise with small volume increments, or intermittently with different inflating volumes, and the curve is constructed thereafter by joining the single static pressure-volume points [42]; 2) the continuous flow method where the chest is inflated and deflated with a constant flow at a rate of 1–2 l/min [33, 41].

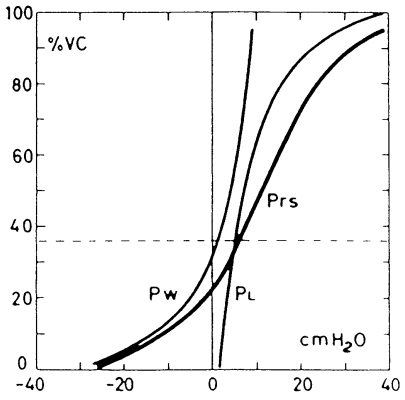

Fig. 1 Static P-V curves of the lung, chest wall, and total respiratory system during relaxation in the supine position in normal human. Note the presence of an upward concavity in the lower portion of curve of the chest wall and the linearity in the corresponding position of the curve of the lung. As a result, an upward concavity is present in the corresponding portion of the curve of the total respiratory system that represents the summation of the pressure of the isolated chest wall and the isolated lung (Reproduced with permission from Agostoni E, Mead J Statics of the respiratory system. In: Fenn WO, Rahan H (Editors) Handbook of Physiology. American Physiological Society (Washington) section 3, vol I, pp 387–409)

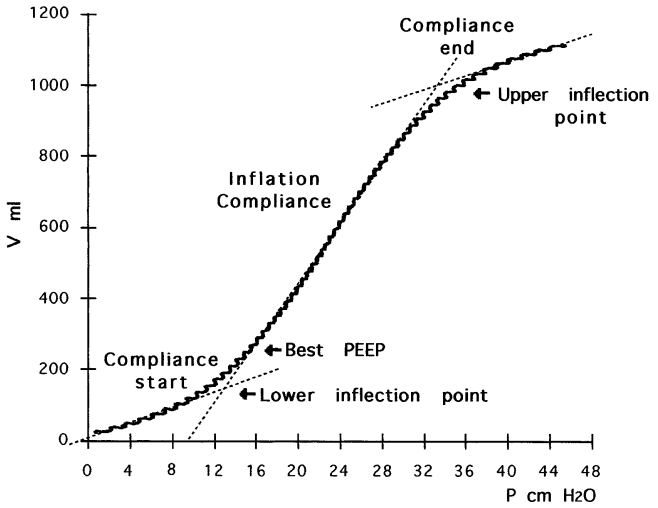

Fig. 2 A typical P-V curve in a patient with ARDS showing a lower and an upper inflection points with the corresponding subdivisions and derived parameters (Reproduced with permission from Mergoni M, Volpi A, Rossi A (1996) Inflection point and alveolar recruitment in ARDS. In: Vincent JL (ed) Yearbook of Intensive and Emergency Medicine. Springer Berlin, pp 556–567)

In the normal subject the lung and the chest wall display different pressure-volume relationships when the volume increases from residual volume to the vital capacity (Fig. 1). In particular, whereas the compliance of the lung is linear at the beginning and in the middle portion of the curve and deflects at the end of the curve, the compliance of the chest wall is low in its initial portion and, thereafter, increases and becomes linear [1]. Consequently the P-V,rs curve, which corresponds to the summation of its isolated components, is sigmoidal in shape and compliance is greater in the midvolume range, where breathing normally occurs.

The P-V,rs curve of the patients with ARDS is also sigmoidal in shape with a straight portion located between an initial and terminal flatter portions.

In this curve (Fig. 2) we can distinguish [2, 24]:

- a starting compliance, which corresponds to the compliance computed in the first 100–150 ml of volume span;
- an inflation compliance, which corresponds to the compliance in the middle straight portion of the curve;
- an end compliance, which corresponds to the compliance in the terminal portion of the curve;
- the total static compliance, which corresponds to the compliance computed as the ratio of the difference in volume to the difference in pressure at the extremes of the inflated volume;
- a lower inflection point (LIP), which is the point of maximum curvature in the initial portion of the curve, corresponding to the interception between the starting and inflation compliance lines;
- the best-PEEP pressure point, corresponding to the pressure where the slope of the curve becomes linear;
- an upper inflection point (UIP), corresponding to the interception of inflation and end compliance lines.

In patients with ARDS total static compliance and inflation compliance are low compared with the normal. This feature is not due to a change in intrinsic elastic properties of the lung parenchyma, but to a reduction of the effective ventilating lung units caused by the filling of alveolar spaces by edema fluid, proteins, cellular debris, and inflammatory cells. In fact specific compliance, which is the compliance normalized for the FRC, is not changed [24], indicating a normal elastic properties of the residual ventilating tissue. The measurement of the compliance of the total respiratory system has, therefore, been regarded as a useful way to follow the evolution of the disease and as a support to clinical decisions [22].

Not only the slope of the curve, but also the UIP and LIP deserve clinical importance, because they have been related to the lung overinflation [2, 8] and alveolar recruitment [42], respectively. We will discuss this latter point.

Lower inflection point on the total respiratory system P-V curve

The LIP on the P-V,rs curve can be due to the lung or to the chest wall components. There are evidences for both these hypothesis.

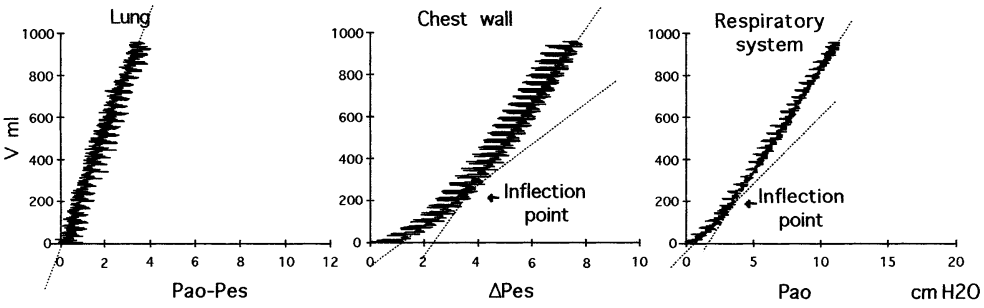

Fig. 3 Partitioning of the respiratory system P-V curve of a patient with acute respiratory failure showing an inflection point on the total respiratory system P-V curve due to the chest wall (Reproduced with permission from Mergoni M, Volpi A, Rossi A (1996) Inflection point and alveolar recruitment in ARDS. In: Vincent JL (ed) Yearbook of Intensive and Emergency Medicine. Springer Berlin, pp 556–567)

Lung

Since Milic-Emili postulated the small airways closure as an explanation for the sequential ventilation at low lung volume [46], it was realized that this would result in a change in shape of the elastic recoil curve of the lung. Sutherland et al. [59] put forward this hypothesis to explain the observed shift to the left of the lung P-V curve at volume lower than FRC, and subsequently Glaiser et al. [30] demonstrated, in excised animal lungs, that the inflection point almost coincided with the closing volume on xenon 133-washout curves. Demedts et al. [16] confirmed this assumption in humans by finding a close correlation between inflection point and closing capacity, even if they were not able to demonstrate an exact coincidence because the closing capacity systematically resulted in an underestimation due to an dead space effect. Finally, airway closure was definitively demonstrated by Engel et al. in 1975 [18].

Studies on the mechanical characteristics of the respiratory system in patients with acute respiratory failure subsequently led to a demonstration of the existence of a LIP in a great proportion of these patients [42]. The finding of a close relationship between a value of PEEP corresponding to the LIP and a sharp increase in the oxygenation [2, 5, 7, 40] was taken as a proof that the LIP was the mechanical counterpart of the recruitment of previously collapsed gas-exchanging units. Further support to this hypothesis came from the demonstration that, ventilating with a value of PEEP lower than LIP, there was a worsening of the structure and of the function of the lung. This result was explained by the deleterious consequences of the continuous opening and closing of the alveoli [49].

Chest wall

As previously reported, a LIP is present on the chest wall P-V curve (P-V,w curve) at low lung volume; nevertheless, the assumption that the lung was responsible for the LIP on the P-V,rs curve has been accepted [51] but never tested in a clinical study. Moreover, studies of the chest wall mechanics have shown that in these patients compliance of the chest wall is reduced compared with the normal [34, 50]. Starting from these observations, Mergoni et al. [45] recently partitioned the P-V,rs curve into the lung and the chest wall in 13 patients with ARF. They found a LIP on the P-V,rs curve at zero positive end-expiratory pressure in all instances. However, in 7 patients the LIP was observed on the chest wall component only (Fig. 3), in 2 patients it was present on the lung component only, and in 4 patients on both lung and chest wall. Interestingly it was found that the changes of the PaO_2 with incremental levels of PEEP were significant only in the group of patients showing the LIP on the lung P-V curve, suggesting a different origin and pathophysiological significance of the LIP found on the P-V,rs curve.

The LIP on the chest wall P-V curve may be explained in several ways. First, the intrinsic mechanical properties of the chest wall may be altered by tissue edema, fluid collection in the pleural and peritoneal cavity, and by abdominal distention [29]. Second, the pressure-volume relationship of the chest wall may be shifted in the lower portion of the curve as a consequence of the decreased lung volume due to the disease process, even taking into account that the reduction in total volume is less than reduction in gas volume due to filling of air spaces with liquid and other material [1]. Third, in the supine position, during anesthesia and muscle paralysis, the diaphragm is displaced upward by gravitational forces. The tension developed across the diaphragm in this way increases the stiffness of the chest wall at low lung volume [37]. The hypothesis that the LIP on the P-V,w curve was related to the lung volume was also supported by the finding that the LIP disappeared from the curve by increasing the level of PEEP [45].

In conclusion, the LIP on the P-V,rs curve can be due either to the lung, reflecting the opening of closed terminal airway and/or alveoli, or to the chest wall, reflecting the changing in chest-wall compliance at low lung volume.

PEEP and alveolar recruitment: the quantitative studies

Even if the use of PEEP in ARDS to improve arterial oxygen content is founded on the assumption that PEEP causes a recruitment of previously closed alveoli, until now only

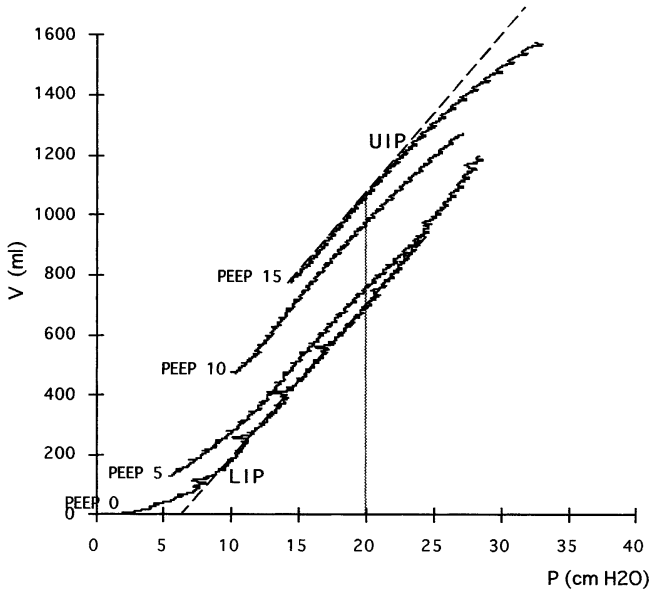

Fig. 4 A representative patient with acute respiratory failure in which the alveolar recruitment with PEEP has been computed with the P-V curves overlapping method. An LIP on the P-V curve at ZEEP and an UIP on the P-V curve at PEEP of 15 cm H_2O are also evident. Alveolar recruitment is computed as difference in volume for the same distending pressure (in this case for a distending pressure of 20 cm H_2O). A significant recruitment is observed by increasing PEEP from 5 to 10 cm H_2O

a few studies have been done to evaluate the amount of the recruitment obtained after application of PEEP.

To our knowledge two methods have been used for the quantitative estimation of the recruitment: the analysis of P-V curves at different levels of PEEP and quantitative CT scan.

P-V curve

This method is based on the fact that if PEEP causes alveolar recruitment, the lung volume is expected to be higher for the same distending pressure. This phenomenon can be studied by overlapping the P-V,rs curves drawn at different levels of PEEP on the same X-Y plot, taking care to compute changes in volume as changes from FRC (Fig. 4). To compute the volume above FRC, the increase in end-expiratory lung volume due to the PEEP (ΔFRC) must be added to the inflated volume. The ΔFRC can be measured by removing PEEP at end-expiration until the static equilibrium volume is reached [8], by subtracting the tidal volume from the volume expired at atmospheric pressure after a standard inspiration [54], by measuring the changes in end-expiratory lung volume with the respiratory inductive plethysmography [62, 63], or by measuring the lung volume at end expiration with an insoluble trace-gas method [35].

Katz et al. [35], studied the effects of 4 different levels of PEEP on lung volume in 13 patients. At PEEP of 18 cm H_2O, end-expiratory lung volume increased by 1170 ml, and the alveolar recruitment, computed as volume difference with respect to the lower level of PEEP, amounted to 444±30 ml.

Rainieri et al. [54] studied the relationships between PEEP and alveolar recruitment in 8 patients with severe ARDS. In 5 patients they found an alveolar recruitment of 230±40 ml at a PEEP level of 15 cm H_2O. In these patients, the P-V,rs curves at ZEEP were characterized by a progressive increase in slope with increasing inflation volume, even if a distinct LIP was present only in two patients. The remaining 3 patients did not exhibit alveolar recruitment, and their P-V,rs curves at ZEEP were characterized by a decrease in slope with increasing volume. So, even if a LIP can not distinctly be detected on the P-V curve, the shape of the curve can predict the effects of PEEP on alveolar recruitment.

In mechanically ventilated patients after open heart surgery, Valta et al. [62] found an increase in alveolar recruitment that proceeded steadily with the increase in PEEP up to a value of 446±123 ml at PEEP level of 15 cm H_2O. They also observed that after removing PEEP, the end-expiratory lung volume remained higher than the corresponding lung volume before the application of PEEP, suggesting a persistent reopening of atelectatic lung units.

Recently the same authors [63] studied the effects of PEEP in nine patients with ARDS and found that, with a PEEP value of 14 cm H_2O, the recruitment was surprisingly small, amounting to only 126±31 ml. In addition a negative correlation was found between alveolar recruitment and static compliance at ZEEP, and between alveolar recruitment and end-inspiratory elastic recoil pressure at ZEEP. In other words, the more severe the disease is (as derived by the value of the static compliance), the smaller the recruitment with PEEP is. A possible explanation for this behavior may be that when lung is severely damaged, even employing conventional tidal volumes or less than conventional tidal volumes, these patients operate relatively close to the flat portion of their static P-V curves, where most of the recruitable lung units have already been recruited.

A frequently reported observation in these [35, 62] and other studies [11] is the upward displacement of the P-V curve in response to the application of PEEP, without a change in slope. This is somehow surprising, because if PEEP causes an alveolar recruitment, the same change in pressure should generate a correspondingly higher change in volume. This phenomenon, also described in a recent study of our group [44] (Fig. 5), can be explained in two ways. First, the compliance may depend principally on structural changes that are not influenced by PEEP, at least during the short term of the study. Second, recruitment and overdistension are contemporary events, and therefore the increase in compliance due to the recruitment may be off-

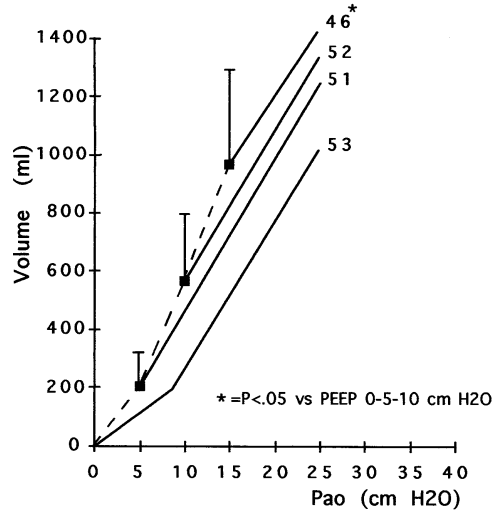

Fig. 5 Mean P-V relationships of the total respiratory system at different levels of PEEP in a group of patients with acute respiratory failure. Squares indicate the mean value of the ΔFRC induced by PEEP. The numbers at the end of the curves indicate the mean value of the inflation compliance of the corresponding curve. The inflation compliance of the curve at PEEP of 15 cm H_2O is significantly lower than inflation compliance of the other curves due to the appearance of an upper inflection point at the higher level of PEEP (Reproduced with permission from Mergoni M, Volpi A, Rossi A (1996) Inflection point and alveolar recruitment in ARDS. In: Vincent JL (ed) Yearbook of Intensive and Emergency Medicine. Springer Berlin, pp 556–567)

set by a decrease in compliance due to the overdistension; once the overdistension prevails, the compliance decreases and an UIP appears on the P-V curve. In line with this observation, the characteristic feature of the alveolar recruitment must be considered the upward displacement of the P-V curve and not the change in the slope, which in fact does not occur. This implies that, if PEEP causes an alveolar recruitment, the changes in lung volume induced by PEEP are greater than the changes predicted by the P-V curve at ZEEP.

CT scan analysis

Gattinoni et al. [24, 25] studied the effects of PEEP on alveolar recruitment by a quantitative analysis on the CT images. They found that increasing PEEP from 5 cm H_2O to 15 cm H_2O, the amount of the normally aerated lung tissue increased from 328±203 g to 475±216 g with a concomitant increase of the gas volume from 1173±553 ml to 1597±707 ml. The amount of recruited lung (computed as difference in the weight of the normally aerated tissue at PEEP 15 cm H_2O from PEEP 5 cm H_2O) was positively correlated with the reduction of the shunt fraction, indicating that units recruited to gas exchange were also perfused both before and after the application of PEEP.

In other studies, Gattinoni et al. found that lung densities in ARDS are located primarily in the dependent regions of the lung [23] and that by changing the body position, the densities within the lung redistribute along the vertical axis [26], suggesting that a gravity-dependent mechanism is in part responsible of the development of the densities. Also, it was demonstrated that the recruitment obtained by PEEP is prevalently distributed in the dependent lung regions where the effects of gravity are more pronounced [28]. In this perspective PEEP seems to act as a force opposing the collapsing effect of an overlying, abnormally heavy, lung tissue [27].

Brunet et al. [8], using the same method of the quantitative CT scan analysis, found that setting a PEEP level corresponding to the LIP, the normally aerated area increased from 141±141 to 239±223 cm^2 corresponding to a 70% increase of the ZEEP area.

Similarly, Dambrosio et al. [12] found that setting PEEP at a value equal to the LIP normal aerated zones increased from 47.3±20.9% to 56.5±13.2% of the ZEEP area.

Lower inflection point, PEEP, and alveolar recruitment

It is current opinion that a close relationship links the LIP to the alveolar recruitment. Nevertheless, some data are not in line with this assumption. For example, Gattinoni [25] did not find any significant difference in recruitment when PEEP level was increased from a value below to a value above the LIP; in fact the alveolar recruitment continued to occur even by increasing PEEP beyond the LIP. Likewise, in a recent work, Mergoni et al. [44] found that alveolar recruitment, measured with the P-V curve method, steadily increased with PEEP, not showing a clear relationship with the LIP. Moreover, it has been found that an alveolar recruitment [54], as well as an improvement in arterial oxygenation [6, 19], can be obtained by PEEP even in patients without a distinct LIP.

Therefore the assumption that LIP always represents an alveolar recruitment may be questioned.

Several hypothesis can be taken into account to explain these findings. First, as outlined above, the LIP on the P-V,rs curve may be due not only to the lung, but also to the chest wall mechanics. Second, the alveolar recruitment may not be an all-or-nothing phenomenon with a single critical pressure at which all closed units suddenly reopen. Instead, it may be a progressive phenomenon that occurs between a low and high pressure limit, and also takes time to complete. This concept is not new: it was first advanced by Lamy et al. in 1976 [39] and recently confirmed by other researchers [60]. Third, there are same discrepancies between the value of the LIP as found in the clinical practice on the static P-V,rs curve (Table 1) and the pressure needed to reopen closed alveoli as derived from experimental studies. If a complete atelectasis is induced by vacuum degass-

Table 1 Values of the lower inflection point measured on the P-V,rs curve reported in the literature.

Authors	Range	Mean ± SD	Reference
Gattinoni	NR	7.7±4	24
Amato*	8–22	NR	2
	6–20		
Brunet	4–16	NR	8
Puybasset	5–12	NR	49
Roupie	5–12	6±4	52
Mergoni	2.5–17.7	7.5±3.9	43

* Values relative to two groups of patients in the same work; NR = no reported

ing or O_2 absorption, 15–25 cm H_2O or more is needed to initiate the lung inflation in isolated canine lung [31]. Higher pressures are needed when the surface tension is increased because of a loss of the alveolar surfactant [43]. In favor of these experimental data are some results from human studies. For example, Gattinoni et al. [28] found that to reopen true atelectatic units in the most dependent zones of the lung, a peak inspiratory pressure up to 50 cm H_2O had to be applied. Recently, Fort et al. [21], using an high-frequency oscillatory ventilation technique, were able to improve oxygenation only if mean airway pressure was increased above 30 cm H_2O.

On the other hand, the low lung volumes and the loss of the surfactant favor the development of the airway closure and from experimental studies it is known that a closed airways reopens abruptly once a critical pressure is reached [43]. This critical pressure ranges from 2 to 10 cm H_2O [40], which is close to the values of the LIP usually recorded in clinical practice (Table 1). As previously reported, small airway closure can be responsible for the LIP on the lung P-V curve; therefore, a recruitment of closed airways as well as of collapsed alveoli can be taken into account to explain the presence of the LIP on the P-V,rs curve.

Conclusions

Alveolar recruitment appears to be a complex phenomenon that is not completely described by a single P-V curve drawn at zero end-expiratory pressure. The exact role of PEEP in this process is not well understood. In fact, at constant VT, increasing PEEP leads to an increase in peak and plateau-pressure, and it may be that these higher pressures correspond to the true recruiting pressure [28, 36, 47]. Even if the recruiting pressures corresponds to the end-inspiratory airway pressure, the role of PEEP is not diminished, because PEEP is necessary to maintain the patency, once it has been achieved. The La Place law may offer an explanation for this. For the La Place law ($P = 2\tau/R$ where P = pressure to stabilize a bubble/alveolus, τ = surface tension at the air liquid interface, and R = radius of the bubble/alveolus) the pressure needed to keep an alveolus open is much smaller than to the pressure needed to open up a collapsed one. Alveolar recruitment, therefore, is probably linked to the build-up of the airway pressure during inspiration, whereas its maintenance is based on the positive pressure level at the end of the expiration. Moreover, the smaller the radius of an alveolus, the higher the pressure required to cause a volume change. In practice, lower pressures are required to ventilate the lung, once the normal alveolar volume has been restored [38].

How high should be the level of the end-expiratory pressure to preserve from the risk of the alveolar derecruitment is not know and only a few studies have dealt with this question [9]. It is important to prevent the tidal opening and reclosure of the alveoli, because the shearing (tangential) forces that develop in this process are recognized as a factor that extends and amplifies the tissue damage in ARDS [49]. On the other hand, with high levels of PEEP and the usual tidal volume, the end-tidal airway pressure can infringe upon the upper inflection zone of the static P-V,rs curve, where overdistension of the ventilated alveoli prevails on the recruitment [57]. Because overdistension also is a damaging factor, the still unresolved fundamental issue of the ventilatory management of the ARDS patients, at least in the early phase of the disease, can be summarized as follows: to reach the lowest peak (or plateau) airway pressure sufficient to obtain the maximal recruitment without putting the lung at risk of barotrauma, and at the same time to set a PEEP high enough to prevent the alveolar reclosure during expiration.

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