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What has been learnt from *P*/*V* curves in patients with acute lung injury/acute respiratory distress syndrome

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What has been learnt from P/V curves in patients with acute lung injury/acute respiratory distress syndrome. S.M. Maggiore, J-C. Richard, L. Brochard. ©ERS Journals Ltd 2003.

ABSTRACT: Mechanical impairment of the respiratory system was recognised soon after the description of acute respiratory distress syndrome. The analysis of the pressure/volume (*P*/*V*) curve of the respiratory system contributed a lot to the understanding of the pathophysiology of acute lung injury and formed the basis for lung protection. The lower and upper inflection points were regarded as points of interest to avoid cyclic derecruitment and overdistension and to optimise ventilatory settings. However, because of the heterogeneity of lung injury, reducing the mechanical properties of the whole respiratory system to a single curve is a schematic approach, which makes interpretation difficult.

New data suggest that alveolar re-inflation occurs along the whole *P*/*V* curve that can, therefore, be considered as a recruitment curve. The lower inflection point has no relationship with alveolar opening and closure and does not indicate the positive end-expiratory pressure needed to prevent alveolar collapse. The shape of the *P*/*V* curve gives information about the extension and the homogeneity of lung injury, indicating the possibility of lung recruitment. The upper inflection point, classically seen as the beginning of overdistension, may also indicate the end of recruitment.

The pressure/volume curve offers the unique opportunity of evaluating alveolar recruitment/derecruitment at the bedside that can be helpful for the identification of optimal ventilatory settings and makes the curve a valuable tool for the ventilatory management of acute lung injury.

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Since its first description, acute respiratory distress syndrome (ARDS) was recognised as a condition characterised by the decrease of lung volume and mechanical abnormalities of the respiratory system [1]. It was therefore tempting to correlate the mechanical impairment of the respiratory system with the severity of the disease and to set the ventilatory parameters accordingly. In 1972, FALKE *et al.* [2] described the changes in dynamic compliance and tidal pressure/volume (*P*/*V*) loops with the application of positive end-expiratory pressure (PEEP) in patients with acute respiratory failure (currently classified as acute lung injury (ALI) or ARDS) [2]. A few years later, SUTER *et al.* [3] showed in a classical paper that the measurement of static or effective compliance (calculated by dividing the tidal volume (V_T) by the difference between end-inspiratory plateau pressure and end-expiratory pressure) could be helpful in determining the PEEP level resulting in optimum cardiopulmonary function. The PEEP level corresponding to the highest static compliance resulted in the best oxygen transport and the lowest deadspace fraction, suggesting optimal alveolar recruitment without overdistension. However, the interaction between ventilatory settings and respiratory mechanics is much more complex and the importance of static compliance was questioned later by the same author who previously showed its value [4]. Indeed, static and dynamic compliance changed with changing V_T and PEEP, because of the nonlinearity of the respiratory system *P*/*V* relationship in ARDS, suggesting that tidal ventilation was displaced along a curvilinear *P*/*V* curve.

Pressure/volume curve in acute respiratory distress syndrome

The *P*/*V* curve is a classical, physiological method used since late 1940s to describe the mechanical properties of the respiratory system [5]. In 1976 BONE [6] showed its usefulness in the diagnosis of ARDS in mechanically ventilated patients. Later studies described the role of the *P*/*V* curve as a monitoring tool in the management of ARDS [7].

The *P*/*V* curve is usually traced above a reference volume which corresponds to the elastic equilibrium volume of the respiratory system. This volume is referred to as the functional residual capacity or, in case of air trapping, the end-expiratory lung volume. Typically, the inspiratory *P*/*V* curve above the functional residual capacity has a sigmoidal shape in ARDS. This is similar to the shape of the curve from residual volume to total lung capacity in healthy humans. However, in the latter case, the slope of the curve in the volume range where tidal ventilation takes place is linear. In ARDS patients, the reduction of the number of normally ventilated alveoli decreases the range where V_T occurs and the entire curve is flattened (fig. 1). The *P*/*V* curve can be considered as consisting of three segments separated by two inflection points (fig. 1). A first segment with low compliance is often identified. It is separated from the intermediate, linear segment with a greater compliance (C_{LIN}) by a lower inflection point (LIP). This steeper part of the curve is followed by an upper inflection point (UIP) beyond which the curve flattens again.

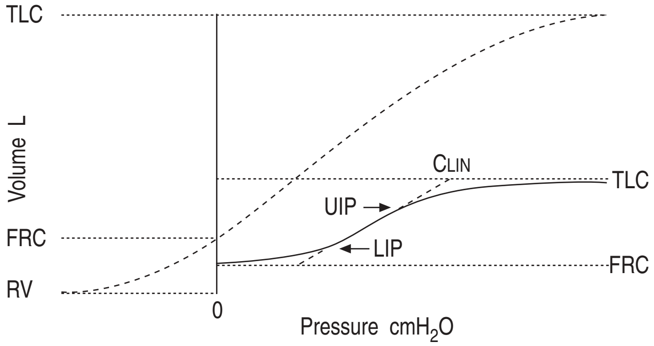

Fig. 1. – Pressure/volume (*P*/*V*) curve of the respiratory system in a healthy subject (- - -) and in a patient with acute respiratory distress syndrome (ARDS) (—). Note the reduction of static lung volumes in ARDS producing the flattening of the curve and the appearance of inflections in the range of tidal ventilation. RV: residual volume; FRC: functional residual capacity; TLC: total lung capacity; LIP: lower inflection point; UIP: upper inflection point; CLIN: compliance of the intermediate, linear segment of the *P*/*V* curve.

A number of studies have tried to clarify the meaning of the inflection points, in the belief that this could have been helpful for the ventilatory management of ARDS. The modifications of the curve induced by different ventilatory settings and during the course of ARDS were also described. Matamis *et al.* [7] using the super-syringe technique, measured *P*/*V* curve above the elastic equilibrium volume of the respiratory system to describe the mechanical abnormalities at different stages of the disease. The authors showed that alterations in respiratory mechanics closely paralleled the natural history of ARDS. In the early stage of ARDS, the curve was characterised by an inflection point in its initial part but the compliance, *i.e.* the slope, of the linear segment had a normal value. In the late stage of the disease ($\geqslant$2 weeks after its onset) when interstitial fibrosis presumably developed, no lower inflection was detectable and compliance was reduced. In accordance with the meaning of the inflection found in healthy subjects below the functional residual capacity, the LIP seen in the early ARDS was thought to reflect the reopening of collapsed airways and/or alveolar units during inspiration [8]. This hypothesis was supported by the fact that setting PEEP just above the pressure at LIP resulted in improvement in gas exchange and intrapulmonary shunt, suggesting optimal alveolar recruitment. Indeed, because of the alveolar instability characteristic of ARDS, collapse is likely to occur when transpulmonary pressure falls during expiration, particularly in the dependent lung areas where superimposed gravitational pressure is higher [9].

The reduced compliance found in patients with ARDS was interpreted as reflecting lung stiffness [10]. Subsequent studies demonstrated that the impairment of the elastic properties of the respiratory system was due to different mechanisms [11–13]. Experimental data from Slutsky *et al.* [11] and Grossman *et al.* [12] showed that the decreased compliance was related to the reduction of aerated lung areas secondary to pulmonary oedema and inflammation. Studies from Gattinoni *et al.* [13] based on computed tomography definitively demonstrated this hypothesis. These authors showed the marked reduction of normally aerated areas in ARDS lung, while the *P*/*V* curve parameters, including CLIN, were correlated with the residual healthy lung zones, and not with the nonaerated tissue. The residual normally aerated lung regions seem to maintain normal intrinsic elasticity, as suggested by the observation that specific compliance, *i.e.* the ratio of measured compliance to lung volume, is not different in ARDS and in normal subjects [13]. Therefore, ARDS can be considered as a restrictive disease ("baby lung" concept), that involves the lung heterogeneously, with coexistence of normal and injured zones. The *P*/*V* curve could explore only the residual, normal lung areas and this accounts for its flattening compared with normal subjects. The heterogeneity of ARDS lung and the nonlinearity of the *P*/*V* relationship also explains why the effective compliance is a poor descriptor of the mechanical properties of the respiratory system.

The UIP is generally identified in healthy subjects at a lung volume ~85–90% of total lung capacity, while in ARDS patients it takes place at a much lower volume. Any further increase of pressure above this point leads to a lower increase in volume, suggesting that stretching of at least some alveolar units has reached its maximum and overdistension is likely to occur. Because several experimental studies demonstrated that mechanical ventilation with high volumes and pressures can be harmful for the lung, attention has been focused on UIP as a possible marker of overdistension. In ARDS patients mechanically ventilated with a mean PEEP of 10 cmH$_2$O, Roupie *et al.* [14] showed that using conventional tidal volumes (9–12 mL·kg^{-1}) the majority (70–100%) of patients had an end-inspiratory plateau pressure exceeding UIP, while a *V*T reduction $\leqslant$6 mL·kg^{-1} was needed to keep plateau pressure below UIP. This was the first study to demonstrate the relevance of *V*T reduction for lung protection.

In summary, several studies based on the *P*/*V* curve allowed a deeper understanding of ARDS pathophysiology to be gained and formed the basis for "lung protection" during the ventilatory management of these patients. LIP was thought to represent the critical pressure needed to reopen the previously collapsed airways and alveolar units, while the UIP was considered as the volume at which alveolar overdistension occurs. Then, lung ventilation occurring below LIP and above UIP could generate end-expiratory collapse and overdistension, respectively, both of which are associated with the appearance and/or the progression of lung injury [15–18]. Setting PEEP above LIP and plateau pressure below UIP was therefore recommended in order to protect the lung from further injury [19]. Recent clinical studies comparing this lung protective approach to a more conventional ventilatory strategy demonstrated the beneficial effects of an individualised ventilatory management based on the *P*/*V* curve on mortality and the progression of pulmonary and systemic inflammation [20, 21].

Interpretation of the pressure/volume curve: a new insight

Recent technical advances and insights into the mechanisms of respiratory system impairment during ALI/ARDS contributed to modify the classical interpretation of the *P*/*V* curve. Using a mathematical model of the ARDS lungs, Hickling [22] demonstrated that alveolar reopening continues on the linear part of the curve, far above LIP, while UIP may indicate that recruitment has ceased during inflation, and does not necessarily indicate only overdistension. Depending on the range of opening pressures, UIP caused by overdistension can be masked if concomitant recruitment continues above the pressure at UIP. Jonson *et al.* [23] confirmed these findings in ALI patients. The authors studied the effect of PEEP on alveolar recruitment and found that alveolar reopening proceeded continuously far above LIP during insufflation. Interestingly and in contrast with classical notions, PEEP-induced alveolar recruitment was associated with a decrease in CLIN. Indeed, the higher compliance at zero end-expiratory pressure (ZEEP) reflects the progressive reopening of alveolar units collapsed at the end of expiration while, when the lung is fully recruited with PEEP, this phenomenon does not occur and CLIN is lower. Later studies corroborated and extended these results [24, 25]. Therefore, LIP cannot be considered as the point where tidal recruitment ends and, as a consequence, it is difficult to use it to optimise alveolar reopening with PEEP. However, PEEP is an expiratory manoeuvre applied to forestall alveolar closure, while LIP is a feature of the inspiratory *P*/*V* curve, eventually related to alveolar opening. To evaluate the relevance of LIP for optimal PEEP setting, it could, therefore, be interesting to evaluate the relationship between LIP and the alveolar closure. MAGGIORE *et al.* [25] studied 16 patients with ALI ventilated with relatively high PEEP (15–20 cmH_2O), and traced *P*/*V* curves from progressively decreasing levels of PEEP. Alveolar derecruitment associated with PEEP decrements was spread almost uniformly up to ZEEP, suggesting that alveolar closure occurred over a wide range of pressures, and LIP was a poor predictor of alveolar closure. These data clearly indicate that LIP may be of limited value for determining the PEEP level required to prevent alveolar collapse. The strong relationship between CLIN of the *P*/*V* curve recorded from ZEEP and the alveolar recruitment induced with 15 cmH_2O PEEP suggests that the compliance of the linear part of the *P*/*V* curve gives an indication of lung recruitability [25]. CROTTI *et al.* [26] in patients and PELOSI *et al.* [27] in an animal model also found that recruitment and derecruitment are continuous processes occurring along the entire inspiratory and expiratory *P*/*V* curves of the respiratory system, respectively, with no relationship with LIP.

Recent studies suggested that other factors could be responsible for LIP. JONSON and SVANTESSON [28] suggested that a marked LIP may be due to the instantaneous reopening of many alveoli having similar threshold opening pressures, as in a homogeneously diseased lung. On the contrary, when the lung injury is heterogeneously distributed, alveolar units with different threshold opening pressures coexist and LIP may be absent. VIEIRA *et al.* [29] correlated the presence and the absence of LIP on the *P*/*V* curve of the respiratory system traced from ZEEP with the distribution of lung disease [29]. When a LIP was present, the lungs appeared to be homogeneously injured (prevalence of poorly or nonaerated zones), and increasing PEEP resulted in a continuous alveolar recruitment without overdistension. On the contrary, in patients without LIP normally aerated and nonaerated lung areas coexisted, while PEEP induced both recruitment and overdistension, which was predominant at higher PEEP levels. Therefore, the presence of a LIP on the respiratory system *P*/*V* curve may simply indicate a homogeneously diseased lung and the need for lung recruitment [22, 23, 29], without giving any indication about the optimal level of PEEP to reach this goal.

The respiratory system consists of two compartments, the lung and the chest wall. The impairment of respiratory mechanics observed in ALI/ARDS patients is usually considered as the expression of lung abnormalities. However, chest wall mechanics may be impaired in these patients and can influence the shape of the *P*/*V* curve of the respiratory system [30–33]. MERGONI *et al.* [31] recorded *P*/*V* curves of the respiratory system, of the lung and of the chest wall in 13 patients with ALI and found that the LIP on the *P*/*V* curve of the respiratory system was due uniquely to the lung in only two patients, while in seven patients it was due exclusively to the chest wall [31]. Interestingly, the application of PEEP improved oxygenation only in those patients exhibiting a LIP on the lung *P*/*V* curve. These findings demonstrate that, at least in some cases, the impairment of the chest wall may explain the abnormalities of respiratory mechanics and the LIP seen on the *P*/*V* curve of the respiratory system. The clinical implications of this are not clear and could be limited. Indeed, the higher value of LIP on the chest wall *P*/*V* curve in the study by MERGONI *et al.* [31] was 4.8 cmH_2O, a value significantly lower than the one usually found on the *P*/*V* curve of the respiratory system in ARDS patients. Other studies did not confirm these results [14, 25, 29], suggesting a minimal influence of the chest wall on the *P*/*V* curve of the respiratory system. Impairment of the chest wall and respiratory system can vary with the underlying disease. RANIERI *et al.* [32] showed that in medical ARDS the chest wall *P*/*V* curve was normal and the *P*/*V* curve of the respiratory system reflected essentially the lung impairment [32]. By contrast, in surgical ARDS the flattening of the *P*/*V* curve of the respiratory system was substantially caused by the impairment of chest wall mechanics secondary to abdominal distension. Similarly, GATTINONI *et al.* [33] reported that patients with a pulmonary ARDS had reduced lung compliance, while patients with an ARDS from extrapulmonary origin showed markedly decreased chest wall compliance and increased intra-abdominal pressure.

Recently, it has been suggested that the *P*/*V* curve can also be influenced by the presence of lung compartments with different time constants. In an interesting study by VIEILLARD-BARON *et al.* [34], the authors reported that, in some patients, the initial, flat segment of the *P*/*V* curve of the respiratory system can be explained with the existence of a lung compartment with a greater time constant. Such a "slow" compartment was caused by regional expiratory flow limitation generating intrinsic PEEP and was responsible for the LIP identified on the inspiratory *P*/*V* curve. The application of moderate levels of external PEEP (6 ± 2 cmH_2O) abolished intrinsic PEEP and LIP, reduced time constants and increased compliance of the respiratory system, suggesting the homogenisation of alveolar ventilation. The *P*/*V* curve of the respiratory system reflects, therefore, different lung regions with heterogeneous mechanical properties and is a composite of multiple regional *P*/*V* curves [35].

In summary, the *P*/*V* curve of the respiratory system can be considered as a recruitment curve, because alveolar re-inflation occurs along the whole curve. The LIP does not indicate the "open-lung" PEEP, but its shape gives information about the extension and the homogeneity of lung injury, eventually predicting the response to PEEP in terms of recruitment and/or overdistension. In addition, compliance of the linear part of the *P*/*V* curve recorded from ZEEP indicates lung recruitability with PEEP. Finally, UIP may indicate the end of recruitment, not necessarily the beginning of overdistension.

Alveolar recruitment/derecruitment: what the pressure/volume curve tells us

ALI/ARDS lung is characterised by a marked heterogeneity, with coexistence of injured and healthy zones. The goal of mechanical ventilation and the difficulty of the ventilatory management of this syndrome is the recruitment of collapsed lung areas, while avoiding the overdistension of the normal alveolar units. In this context, the evaluation of alveolar recruitment was an important step for interest in the *P*/*V* curve [23, 25, 36]. The assessment of recruitment requires the alignment of *P*/*V* curves recorded from different PEEP levels on the same *P*/*V* diagram (fig. 2). A passive expired spirogram is performed from each PEEP level to determine the starting point of each *P*/*V* curve related to the relaxation volume of the respiratory system, which is assumed to be constant. The recruited volume is indicated by the volume shift between *P*/*V* curves, denoting a greater lung volume for the same level of airway pressure. RANIERI *et al.* [36, 37] used this method to quantify PEEP-induced alveolar recruitment [36] and the role of volume history, *i.e.* V_T, on the amount of recruitment with PEEP [37]. Later, such a technique has been used to analyse the mechanisms of alveolar reopening and collapse and their

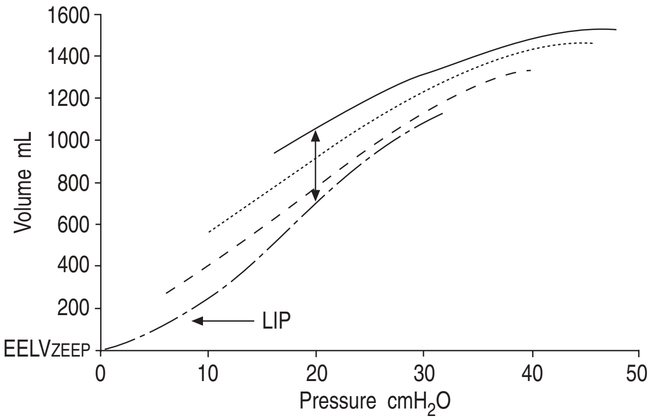

Fig. 2. – Multiple pressure/volume (*P/V*) curves of the respiratory system recorded from different levels of positive end-expiratory pressure (PEEP) (– – –: PEEP 5; ·········: PEEP10; —: PEEP15) and from zero end-expiratory pressure (ZEEP; – · – ·), and related to the elastic equilibrium volume of the respiratory system at ZEEP (EELVZEEP). The curves are aligned on the same *P/V* diagram after correcting the starting points of each PEEP *P/V* curve for the volumes measured during passive expired spirograms performed at each PEEP level. The upward shift of PEEP *P/V* curves indicates alveolar recruitment. The recruited volume with 15 cmH_2O PEEP (double-headed arrow), compared to ZEEP, is quantified by the volume difference between the curves, for the same level of airway pressure (20 cmH_2O in this example). In other terms, when PEEP is applied, for the same level of airway pressure, lung volume is greater than without PEEP, suggesting the reopening of some alveolar units previously collapsed at ZEEP. Note that recruitment continues far above the value of pressure at the lower inflection point (LIP) and above to the upper inflection point. The different *P/V* curves tend to join at higher lung volumes, suggesting that the maximal lung volume is approached (modified from [25]).

relationship with LIP [23, 25]. To analyse the effect of *V*T on alveolar recruitment, RICHARD *et al.* [24] have recently measured alveolar recruitment in 15 ALI patients mechanically ventilated with PEEP set at LIP. The reduction of *V*T according to the actual recommendations (6 $mL \cdot kg^{-1}$) induced a significant derecruitment compared to a conventional *V*T (10 $mL \cdot kg^{-1}$). A recruiting manoeuvre (two consecutive insufflations at 45 cmH_2O applied for 15 s) reversed this difference, increasing recruitment with the low *V*T but with no effect with the conventional *V*T. This suggests that such recruitment manoeuvres are effective when the lung has previously been derecruited, as in the low *V*T strategy. Increasing PEEP (4 cmH_2O above LIP) prevented the derecruitment with the low *V*T and induced a greater recruitment with both tidal volumes, reinforcing the idea that LIP does not indicate the PEEP required to prevent alveolar collapse. These results indicate that both PEEP and *V*T play a role for alveolar reopening. Alveolar recruitment could proceed up to the end of tidal insufflation and, therefore, could depend upon the end-inspiratory pressure resulting from a given PEEP and *V*T. From the results of the study by RICHARD *et al.* [24] it is difficult, however, to understand if the derecruitment associated with low *V*T ventilation is a result of the low *V*T *per se*, or of the reduction in plateau pressure that occurs when *V*T is reduced with a constant PEEP level. This issue has been elegantly addressed by the same authors [38], who measured alveolar recruitment with 3 ventilatory strategies: 1) PEEP set at LIP (11 cmH_2O) with a *V*T of 6 $mL \cdot kg^{-1}$; 2) PEEP set at LIP with a *V*T of 10 $mL \cdot kg^{-1}$; and 3) high PEEP (14 cmH_2O) with a *V*T 6 $mL \cdot kg^{-1}$, keeping the end-inspiratory plateau pressure similar to condition 2. For the same plateau pressure, recruitment was significantly greater when a high PEEP/low *V*T was used, compared to the low PEEP/high *V*T strategy. Therefore, the derecruitment seen with low *V*T ventilation is a result of the reduced plateau pressure, not of a low *V*T *per se*. For a given end-inspiratory plateau pressure, alveolar recruitment can be much more influenced by PEEP than by the size of the *V*T itself, as previously suggested by CROTTI *et al.* [26].

Conclusions

The pressure/volume curve of the respiratory system has contributed to a better understanding of mechanisms of lung impairment during acute lung injury/acute respiratory distress syndrome and of complex rules governing alveolar recruitment and derecruitment, playing a central role in the development of the concept of lung protection. The simplification of the composite characteristics of mechanical abnormalities of the respiratory system in acute lung injury/acute respiratory distress syndrome makes the interpretation of the curve difficult. In the light of the new advances, the pressure/volume curve gives information about morphology of lung injury and lung recruitability and offers the unique possibility of evaluating alveolar recruitment/derecruitment at the bedside. This information can be helpful for characterising the stage of the disease and the identification of optimal ventilatory settings, making the pressure/volume curve a valuable tool for the ventilatory management of acute lung injury/acute respiratory distress syndrome patients.

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