Acute lung injury/acute respiratory distress syndrome pathophysiology: what we have learned from computed tomography scanning

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Current Opinion in Critical Care 2008, 14:64–69

Purpose of review
Although many years have passed since its first application in acute respiratory distress syndrome, computed tomography remains widely employed for research and clinical purposes. Here, we review recent findings derived from computed tomography scanning during acute respiratory distress syndrome, particularly concerning setting positive end-expiratory pressure and mechanisms of ventilator-induced lung injury.

Recent findings
Several studies have provided evidence for the validity of monitoring dynamic mechanics of the respiratory system to estimate the balance between beneficial (i.e. reduction of alveolar derecruitment) and harmful (i.e. lung hyperinflation) effects, consequent to positive end-expiratory pressure increase. The combination of different respiratory variables to estimate lung recruitment has become a more accepted approach. Computed tomography scanning has provided important evidence of lung hyperinflation even after the use of low tidal volume in a specific category of patients. Alternative techniques, such as electrical impedance tomography and lung ultrasound, appear as promising tools potentially available at the bedside.

Summary
As far as setting positive end-expiratory pressure is concerned, further randomized clinical studies are warranted to verify the pathophysiologic findings recently observed with computed tomography scanning. Similarly, the safety of the widespread use of low tidal volume should be brought into question, possibly pointing out a category of patients who may benefit from alternative techniques of respiratory support.

Keywords
acute lung injury, acute respiratory distress syndrome, computed tomography, positive end-expiratory pressure, ventilator-induced lung injury

Curr Opin Crit Care 14:64–69

1070-5295

Introduction

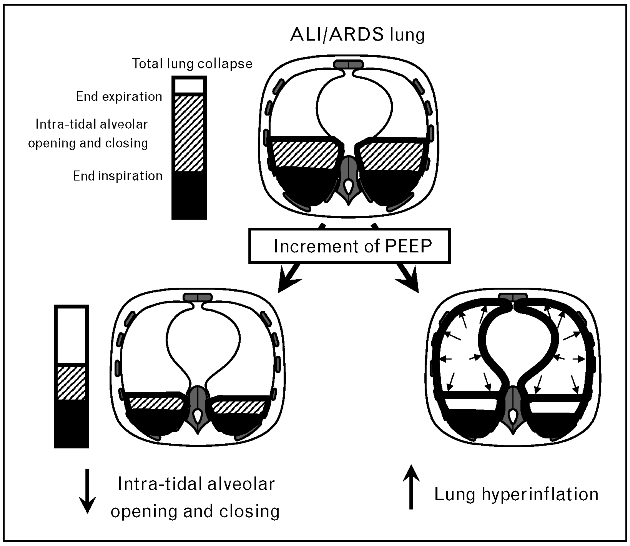
More than 20 years have passed since the first manuscripts reporting the application of computed tomography (CT) for studying patients affected by acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) [1,2], and many steps towards a better understanding of its pathophysiology and clinical treatment have been made. The use of CT scanning has now gained great popularity among both investigators and clinicians, not only for research purposes, but also in current clinical practice for the treatment of this syndrome [3–6], whose incidence in intensive care units is still elevated [7,8]. Moreover, some recent works, both from our group and others [9,10•,11••–13••], have once again brought to the attention of the scientific community how the application of this technique might be useful to investigate and thereby set mechanical ventilation with particular regard to two main issues: the possibility of the collapsed lung to be recruited, i.e. the potential for lung recruitment, and setting positive end-expiratory pressure (PEEP). Nonetheless, many problems still remain unsolved and have recently been investigated with the use of CT. Here, we will briefly summarize recent studies that have applied CT scanning to study ALI/ARDS, with particular regard to the setting of PEEP, the mechanisms of ventilator-induced lung injury (VILI) and the comparison of CT scanning with newly available technologies for studying lung imaging.

Setting of positive end-expiratory pressure

Although the use of a positive level of end-expiratory pressure has been around since the beginning of ventilatory treatment of ALI/ARDS [14,15], the correct method for its setting is still unclear [16,17]. There is no doubt that the application of a higher level of PEEP most of the time has beneficial effects in terms of gas exchange. In contrast, when PEEP is considered a beneficial tool to improve survival of ALI/ARDS patients, the rationale for its benefit is not at all straightforward. In fact, as the ARDS lung is usually characterized by the presence of both a normally aerated and a nonaerated region, we should not forget that the applied PEEP acts similarly onto these two different lung areas. As a consequence, when PEEP increases, on the one hand, it reduces the amount of lung parenchyma undergoing intra-tidal cycling opening and closing, by keeping open a larger portion of alveoli, and, on the other hand, it determines a greater inflation of the already-open alveoli, exposing them to the potentially harmful risk of hyperinflation (Fig. 1).

Many studies have tried to elucidate the optimal way to set the PEEP level, balancing its beneficial and detrimental effects. In particular, several investigations have recently studied the possibility of employing dynamic respiratory mechanics for this purpose. In an experimental model of ALI induced by lung lavage, Suarez-Sipmann *et al.* [10•] investigated the efficacy of a breath-by-breath monitoring of the dynamic compliance of the respiratory system as a parameter to detect, at the bedside, the beginning of lung collapse, thereby indicating the optimal level of PEEP. By applying a decremental PEEP trial, the authors observed a high coincidence between the levels of pressure at which nonaerated lung tissue markedly increased, as measured by CT scan, and the level of pressure at which the dynamic compliance of the respiratory system decreased. Based on the same reasoning, Carvalho *et al.* [11••] hypothesized that setting PEEP according to the minimization of the respiratory system elastance could have balanced the role of PEEP in reducing alveolar derecruitment with a minimal increase in hyperinflation. In six animals, after induction of ALI by intravascular infusion of oleic acid, the authors observed that the PEEP level at which the minimal respiratory elastance was detected corresponded to the greatest amount of normally aerated lung areas, in association with the lowest amount of both lung atelectasis and hyperinflation. Finally, Bellardine Black *et al.* [12••], in a similar experimental model of ALI, elucidated the feasibility of estimating variations in lung heterogeneity from the analysis of the frequency responses of both resistance and elastance of the respiratory system. By applying whole-lung CT scans, the authors observed that a level of PEEP between 15 and 17.5 cmH_2O, defined as ‘optimal’, led to a marked alveolar recruitment without a significant hyperinflation, and that such a level simultaneously minimized parameters of dynamic respiratory mechanics related to mechanical heterogeneity. Of note, the same level of PEEP maximized systemic arterial oxygenation and the compliance of the respiratory system, and minimized the arterial partial pressure of carbon dioxide ($PaCO_2$), while keeping constant minute ventilation.

Figure 1 Schematic representation of the effects of the increase of positive end-expiratory pressure (PEEP) on the lung parenchyma during acute lung injury/acute respiratory distress syndrome (ALI/ARDS)



As shown in the upper panel, the ARDS lung is commonly characterized by the simultaneous presence of a normally aerated (white) and a collapsed (black) lung area. During each tidal breath, the end-inspiratory pressure will decrease the amount of collapsed lung by recruiting alveolar units. At the end of expiration, a portion of the recruited alveoli will collapse again, thereby generating a ‘cycling alveolar opening and closing’ process. The increase of PEEP during volume-controlled ventilation with a constant tidal volume may determine two opposite effects: on the one hand (lower left panel), it will decrease the amount of lung tissue undergoing cycling opening and closing by increasing the amount of alveolar units kept open at the end of expiration, and, on the other hand (lower right panel), it will augment the degree of hyperinflation of the normally aerated lung region.

As shown by the study of Bellardine Black *et al.* [12••], and other studies [9,18], the concept of combining variations of different respiratory variables, such as the arterial partial pressure of oxygen (PaO_2), $PaCO_2$ and respiratory mechanics, to detect lung collapse or lung recruitment is being applied more often both in research and clinical studies. After we had hypothesized that the presence of an increase in PaO_2, a decrease in $PaCO_2$ and an improvement in the respiratory system compliance could have indicated patients with a higher potential for lung recruitment, we were disappointed by the low specificity of estimating the higher maximal potential for lung recruitment, as detected by whole-lung CT scanning [9]. Nonetheless, we have no doubt that this approach is based on a more solid rationale than PaO_2 variations alone [19]. Dueck [20•], in an elegant review on the contemporary presence of lung recruitment and hyperinflation after PEEP application, clearly suggests the necessity of analyzing both PaO_2 and $PaCO_2$ variation during PEEP setting in order to characterize values balancing the two phenomena.

A further important step recently shown is the characterization of PEEP as an expiratory maneuver. In fact, the application of a higher level of positive pressure at end expiration does not result, *per se*, in lung recruitment, but rather it enhances the amount of lung kept open at end expiration after it has been previously recruited during inspiration [21]. Jeon *et al.* [22•], in an oleic acid-induced lung injury model, compared two different methods of setting PEEP based on the inflation and the deflation limbs of the pressure–volume (*P*/*V*) curve of the respiratory system. The authors observed that the application of a PEEP level set on the deflation limb of the *P*/*V* curve was associated with a better PaO_2 and a lower shunt fraction as compared to a PEEP level set on the inflation limb, paralleled by a decrease in the amount of lung atelectasis and a minimal degree of hyperinflation. Although these findings are of some interest, the design of this investigation may appear problematic. In fact, the sequence of the two levels of PEEP applied was not randomized, the two resulting levels of PEEP did not differ and the improvement of PaO_2 detected at the PEEP set on the deflation limb was paralleled by a decrease in cardiac index, which is an independent factor leading to an improvement in PaO_2. It is therefore conceivable that the significant improvement in PaO_2 observed at the PEEP level set on the deflation limb was caused by the recruitment maneuver performed between the inflation and the deflation of the *P*/*V* curve. Finally, although important to provide the overall picture of the behavior of the entire lung parenchyma, *P*/*V* curve measurement is not without limitations, such as the impossibility of describing regional effects of mechanical ventilation, as well as possible artifacts due to oxygen consumption, blood volume shift, etc. [23,24]. Nonetheless, the study by Jeon *et al.* [22•] has the merit of clearly underlying the rationale of setting PEEP during a decremental PEEP trial, as shown by Suarez-Sipmann *et al.* [10•] and Carvalho *et al.* [11••].

Mechanisms of ventilator-induced lung injury

Since the first studies on the effects of mechanical ventilation on the lung parenchyma, two main mechanisms have been identified as responsible for the development of VILI: intra-tidal and cycling alveolar opening and closing [25,26], and lung hyperinflation [27,28]. In the past 20 years, several investigations have focused on this issue, aiming at elucidating the possible pathophysiology, both from a molecular/biological as well as from a micro-mechanic point of view, and focusing at the same time on the possible influence on the clinical outcome of ALI/ARDS patients [29]. From this perspective, it is important to emphasize how the entire research on this topic may represent one of the best examples of translational research in the field of critical care medicine, with particular regard to the harmful effect of lung hyperinflation and tidal volume setting [30].

Although some clinical studies have confirmed a similar perspective for the harmful effect of intra-tidal cycling alveolar opening and closing and the benefit of an open-lung ventilatory strategy [26,31–33], the game is still ongoing in this regard, in particular if we consider the contrasting effects of PEEP on the lung parenchyma and the heterogeneity of the disease during ALI/ARDS. In this regard, Terragni *et al.* [13••], in a very elegant study, have provided important insights by applying whole-lung CT scanning. In 30 ALI/ARDS patients, in which mechanical ventilation was set according to a low tidal volume strategy (6 ml/kg of predicted body weight), and in which two whole-lung CT scans were performed both at end expiration and at end inspiration, the authors identified two different clusters of patients, according to their behavior in response to the low tidal volume employed: patients ‘less protected’ from mechanical ventilation, in which a significant amount of tidal hyperinflation was detected, and patients ‘more protected’, in which a lower degree of hyperinflation was observed at end inspiration. Of note, patients who were ‘less protected’ appeared to have a greater amount of nonaerated lung tissue at end expiration as compared to patients ‘more protected’ from mechanical ventilation, suggesting the extreme importance of the size of the relatively healthy portion of the lung for the safety of mechanical ventilation (i.e. the ‘baby lung’ compartment [34]). As a consequence, the cluster of ‘less-protected’ patients revealed, at a low tidal volume ventilatory strategy applied, a higher degree of pulmonary inflammatory cytokines and a lower number of ventilator-free days. The study therefore concluded that a particular category of ALI/ARDS patients may not be protected from VILI even with the limitation of tidal volume to 6 ml/kg of predicted body weight, these patients being characterized by a greater amount of lung collapse and a smaller portion of aerated lung tissue. Although some of these findings appear to be partially different from what has been previously reported by our group while studying the potential for lung recruitment during ALI/ARDS [9], this study has the great merit of showing that the overall application of the ARDSnet ventilatory strategy may not be safe in some patients, which may rather benefit from alternative forms of respiratory support, such as extracorporeal lung support [35].

The comprehension of how tidal hyperinflation and intra-tidal alveolar opening and closing determines an injury to the lungs during mechanical ventilation, and how these mechanisms may affect survival of ALI/ARDS patients, will certainly be one of the major aims of research in the near future, and experimental research will probably still play an important role, as recently shown by Karmrodt *et al.* [36•]. By studying two different experimental models of ALI, the authors investigated the nature of lung derecruitment, aimed at further understanding whether the nonaerated lung compartment characterizing ALI/ARDS is formed mostly by fluid-filled or collapsed lung tissue [37]. After the induction of ALI with either lung lavage (favoring lung collapse by surfactant depletion) or intravenous injection of oleic acid (favoring alveolar flooding by the increased permeability of the alveolar–capillary membrane), they observed a similar decrease of nonaerated lung tissue from 5 to 50 cmH_2O airway pressure applied during continuous positive airway pressure. The authors therefore concluded in favor of alveolar collapse as the main characteristic of nonaerated lung areas also after the induction of lung injury by oleic acid administration, thereby underlying the nature of cycling alveolar collapse as part of lung derecruitment during tidal breathing.

Another important step towards a better understanding of the mechanical and biological pathophysiology of VILI relies on the introduction of genomics in experimental research on ALI, as documented by several recent studies [38,39]. Simon *et al.* [40••], in a very elegant and well-designed investigation, set out to elucidate the different genomic responses related to the development of ALI during mechanical ventilation in different anatomical lung regions and to relate these differences to the specific mechanisms characterizing those regions (i.e. nondependent vs. dependent lung regions and lung apex vs. base) as detected by CT scanning. Four hours after the induction of a unilateral ALI by lung lavage, the authors observed a different pattern of gene upregulation and downregulation between lung regions located at the lung apex and base, as well as between nondependent and dependent lung regions, which were observed as being subjected to intra-tidal alveolar opening and closing. In particular, genes related to cell adhesion and blood coagulation were observed to be upregulated both in the dependent and nondependent lung regions, while the former group was downregulated at the lung base, as compared to the lung apex, and the latter group appeared to be upregulated in both lung regions. In contrast, genes related to inflammation and immune responses and those related to the cellular response to DNA repair appeared to be upregulated only in dependent lung regions, where a large amount of lung tissue appeared to be undergoing cycling recruitment and derecruitment during tidal breathing. On the whole, these findings once again demonstrate how the heterogeneity of ALI/ARDS may affect the onset of different mechanisms of VILI peculiar to different anatomical lung regions, through the development and the potential activation of different cellular pathways.

New technologies for lung imaging

Although the use of CT scanning has become more widespread both for research and clinical purposes, and at the moment many groups have started to employ CT for clinical management of ALI/ARDS, some well-known limitations (such as transportation to the CT scan facility, exposure to radiation, difficulty of following the dynamic process of ventilation) keep CT scan from being routinely applied to all patients and all over the world [41]. For these reasons, the introduction of new technologies aimed at studying lung imaging at the bedside has always been considered as an improvement. Recently, two technologies have gained great attention, and have been extensively tested both in experimental and clinical settings: electrical impedance tomography (EIT) and lung ultrasound.

In a large review on the recent literature on this topic, Putensen *et al.* [42•] extensively summarize the characteristics, advantages and limits of the bedside application of EIT for lung imaging during ALI. Through the use of surface electrodes applied circumferentially to the thorax, and through measurements of the modification of thorax impedance after the injection of small currents and change in pulmonary aeration, EIT allows a direct estimate of regional lung ventilation during tidal breathing. It has therefore the advantages of being a radiation-free technique, minimally invasive and applicable at the bedside. Unfortunately, its spatial resolution is generally lower than that obtained from CT scanning or other techniques of lung imaging, such as MRI or PET [43]. Moreover, this limitation may become even more important as the region of interest of the analysis proceeds deeper into the lung parenchyma, far from the skin electrodes. Different studies for EIT validation have been performed in experimental and clinical settings, both in healthy and injured lungs [42•,44,45], comparing EIT measurements and analyses obtained with CT scanning, generally resulting in a good agreement between the two techniques. Although further studies are still needed to allow its routine application at the bedside, EIT certainly represents a promising alternative technique for lung imaging.

Similar to EIT, lung ultrasound is gaining greater attention for routine assessment of lung imaging in several, different clinical scenarios, as extensively reviewed by Bouhemad *et al.* [46•]. Based on the convenience of its employment, as well as the possibility of its repetition to follow the evolution of a specific clinical situation, chest ultrasound is often being applied to initially assess the lung status in severely hypoxic patients, as it allows detecting particular situations such as pleural effusion, pneumothorax and lung contusion. Moreover, the application of lung ultrasound has been recently investigated to quantitatively assess alveolar recruitment in patients affected by ventilator-associated pneumonia [46•]. Of note, a good correlation was observed between lung recruitment as assessed by CT scanning and the modification in the 'ultrasound score', a parameter estimating lung re-aeration. Notwithstanding these promising findings, lung ultrasound appears to have some limitations that probably will never be overcome for its routine use in intensive care medicine, such as the intra- and interobserver variability of the procedure, the impossibility of correct imaging in particular subjects such as obese patients (due to the extreme thickness of the rib cage), and the impossibility of detecting lung hyperinflation. Future studies are warranted to actually show the potential advantages of a routine application of lung ultrasound in ALI/ARDS patients.

Conclusion

Although the limitations of employing CT scanning for studying and guiding the clinical management of ALI/ARDS patients have been known since its first application in intensive care medicine, this technique remains widely applied both for research and clinical purposes. The further steps recently made towards a better understanding of the effects of PEEP on lung parenchyma, as well as the possible mechanisms leading to VILI, provide a solid base on which it will be possible to hypothesize future studies. Among others, the usefulness of monitoring dynamic mechanics of the respiratory system while changing PEEP, as well as the role of tidal hyperinflation even with the application of a low tidal volume strategy, represent novel and important findings obtained with CT scanning. In the next few years, further investigations will tell us whether it will be possible to apply alternative techniques for lung imaging, obtaining a comparable 'quality' of information as derived by CT.

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