VIA MEDICA

REVIEW ARTICLES

Anaesthesiology Intensive Therapy
2013, vol. 45, no 3, 164–170
ISSN 1642–5758
DOI: 10.5603/AIT.2013.0034
www.ait.viamedica.pl

Ventilator-associated lung injury

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Abstract

Mechanical ventilation of disease-affected lungs, as well as an inadequate ventilatory mode of initially healthy lungs, can cause significant changes in lung structure and function. To differentiate between these processes, two terms are used: ventilator-associated lung injury (VALI) and ventilator-induced lung injury (VILI). In both cases, lung injury primarily results from the differences in transpulmonary pressure, which is a consequence of imbalance between lung stress and strain. The present study focuses on changes in lung structure and function due to this imbalance. In this context, barotrauma, volutrauma and atelectrauma are interpreted and the importance of signal transduction, which is a process for inducing local and systemic inflammatory responses (biotrauma), is determined. None of the assessed methods for reducing VALI and VILI has been found to be useful; however, studies evaluating oscillatory ventilation, liquid ventilation, early ECMO, super-protective ventilation or noisy ventilation and administration of certain drugs are underway. Low tidal volume ventilation and adequately adjusted PEEP appear to be the best preventive measures for mechanical ventilation in any setting, including the operating theatre. Furthermore, the present study highlights the advances in VILI/VALI prevention, which are derived from a better understanding of pathophysiological phenomena.

Key words: mechanical lung ventilation, ventilator-associated lung injury; mechanical lung ventilation, lung protective ventilation

Anaesthesiology Intensive Therapy 2013, vol. 45, no 3, 164–170

Mechanical lung ventilation is the basic tool for treating critically ill patients in intensive care units (ICUs). It is also a crucial element used in general anaesthesia. As with any medical procedure, mechanical ventilation is likely to cause complications. The most serious complications include lung injury during ventilation and the subsequent development of inflammation, which can spread to distant organs and considerably affect treatment outcomes [1]. In the 1970s, the term ventilator-induced lung injury (VILI) was introduced to define these adverse effects. VILI has recently been used concurrently with ventilator-associated lung injury (VALI), although the terms are not interchangeable. VALI refers to exacerbation of pre-existing lung injury due to factors related to mechanical ventilation, whereas VILI is used for injury to previously unaffected lungs or intentional experimental lung injury in animals [2, 3].

BAROTRAUMA AND VOLUTRAUMA

Barotrauma was the first widely recognised element of VILI. In 1745, Fothergill warned against barotrauma in his study on attempted lung ventilation during resuscitation [4]. The clinical and radiological features of barotrauma include pneumothorax, pneumomediastinum, interlobular emphysema and subcutaneous emphysema of the neck, face, thorax or scrotum. These changes may occur individually or in various pathological sequences [5–7]. The transfer of air outside the alveoli may be a manifestation of weakened pulmonary connective tissue due to the underlying disease and can be caused by non-physiological pressures used during mechanical ventilation [3]. The term "barotrauma" has been widely used in connection with VILI; currently, the severity of pulmonary emphysema (pulmonary hyperaeration) induced by high tidal volumes is believed to be the

more important injuring factor than the airway pressure. These conclusions were reached following the studies on trumpeters who, in order to produce sound from an instrument, reach airway pressure up to 150 cm H_2O (14.7 kPa) without episodes of acute barotraumas. Interestingly, the incidence of barotrauma was comparable in both groups of the ARDS Net study [7]. The authors noted a 10% incidence of barotrauma in the group of low tidal volumes (V_T = 6 mL kg^{-1} PBW (predicted body weight)) and 11% incidence in the group with V_T = 12 mL kg^{-1} PBW during the first 28 days of observation. The term "volutrauma" became popular among clinicians following the turning point study by Dreyfuss and colleagues [8], who subjected healthy rats to high-pressure ventilation with their chests and abdominal cavities bounded (to immobilise the trunk and limit the amplitude of respiratory movements). Under such conditions, V_T was moderate and airway pressures were extremely high; however, no lung injury was observed. In contrast, the lungs of animals ventilated without restrictions to the trunk and chest walls (lower chest wall elastance) reached a very high V_T at given pressures, and the observed features of lung injury were dramatic. This spectacular study led to the conclusion that volutrauma, rather than barotrauma, was the primary VILI determinant [8].

To discuss the presented VILI theories, it is crucial to determine the transpulmonary pressure (P_L), which acts on lungs during ventilation (both mechanical and spontaneous), or the difference between the airway pressure (P_{aw}) and pleural pressure (P_{pl}). Explaining the Dreyfuss's experiment from this point of view and bearing in mind that the actual force expanding the lungs is P_L (and not P_{aw}), we noted that pleural pressure considerably increased during artificial enhancement of chest wall elastance. Therefore, despite extremely high airway pressures, we observed a suitably high pleural pressure and a normal difference expressed as P_L, which means that we observed no injury to the lung structure [6, 8]. It should be stressed that for a given airway pressure, the development of VILI will depend on the generated transpulmonary pressure. Therefore, the name "volutrauma" is more precise; however, in practice, both terms in question are closely related and often used interchangeably or jointly, i.e., baro/volutrauma [5, 6].

The forces that develop in the lung structure in response to the straining and centrifugal transpulmonary pressure may be defined as stress [6, 9, 10]. In contrast, if the lung deformation due to tidal volume is considered in relation to its resting position, strain occurs [6, 9, 10]. Strain may be defined as a ratio of gas volume supplied during inspiration to the volume of aerated lung (only the open pulmonary alveoli) receiving this portion of gas [10, 11]. Under physiological conditions, stress and strain are almost linearly dependent:

$$\text{STRESS} = K \times \text{STRAIN},$$

where K is the specific lung elastance equal to transpulmonary pressure appearing at V_T = FRC) [6, 9, 10].

Published reports have demonstrated that specific lung elastance for the described value of 2 × FRC (lung volume at double FRC) is approximately 13 cm H2O (1.3 kPa) both in healthy and ALI/ARDS-injured lungs [10, 12]. Even in cases of lung injury, barotrauma (stress) and volutrauma (strain) remain in a constant relation described by the equation [6, 10]. It has thus been assumed that the clinical equivalent of stress is transpulmonary pressure, whereas the clinical equivalent of strain is the ratio of volume change (ΔV) to FRC [9, 12]. For a practical understanding of this analysis, we should note that the plateau pressure in the airways is not and can never be a substitute of pulmonary stress and that experiments indicate similar values of stress despite completely different (high and low) tidal volumes applied and vice versa. This observation is attributable to the variability of the ratio of pulmonary elastance to the sum of lung and chest wall elastance in individual groups of patients. Moreover, the above deliberations show certain inaccuracy of the ARDS Net results regarding global, safe threshold of $P_{plateau}$ and V_T and indicate that optimal ventilatory parameters must be individually determined according to measurements of lung biomechanics [9, 10, 12].

BIOTRAUMA AND MECHANOTRANSDUCTION

The concept of ventilation-related lung injury recently presented in the literature assumes that lungs are injured when the applied forces (stress/strain) are strong enough to cause mechanical destruction of the anatomical lung structure. However, numerous experimental studies conducted since the early 1990s suggested that even without tissue discontinuance, the forces acting during ventilation may induce the release of proinflammatory cytokines, recruitment of leucocytes and local initiation of inflammatory processes. This type of biological reaction in response to mechanical forces is defined as biotrauma [3, 5, 6, 9, 13, 14]. According to the experimental data, the biotrauma hypothesis assumes that lung injury caused by harmful strategies of mechanical ventilation is triggered by the release of proinflammatory mediators and the excessive activation of the immune system. Attention has also been focused on the mechanisms involved in ventilation-associated activation of the immune system, which results in the formulation of mechanotransduction theories [6, 14]. The term mechanotransduction is used to describe intracellular signalling processes that appear in response to external mechanical forces. Signalling changes pertain to cells of intact structure and integrity. Cell injury or its critical deformation damages this signalling

pathway, whereas the cascade of inflammation is caused by a different mechanism. The above processes leading to biotrauma cause diverse biological responses, which most commonly include the action of oxygen free radicals, cellular mechanisms of growth and apoptosis, activation of coagulation cascade and stimulation of various elements of the immune system, which lead consequently to the cascade of inflammation. An early and frequent manifestation of biotrauma is the recruitment of neutrophils from the vascular bed to the lungs and their prolonged survival in response to the release of cytokines and chemokines from epithelial cells and alveolar macrophages. The production of cytokines is primarily affected by activation of NF-κB, which becomes the major factor of modification of nucleic acid sequence in the cell nucleus and synthesis of inflammatory factors (TNF-α, IL-1β, IL-6, IL-8) [3, 13, 14].

ATELECTRAUMA

Too low end-expiratory lung volume may be related *inter alia* to cyclic opening and collapse of unstable lung units, which is promoted by ventilation with zero or inadequate PEEP. The repeated opening and collapse of the alveoli and bronchial tree end segments generate forces tangent to alveolar basement membranes (sometimes not aptly referred to as "cutting"). The entire phenomenon of multidirectional changes in stress is called atelectrauma. In this context, the detrimental effects of ventilation may be alleviated by the application of PEEP to prevent the cyclic derecruitment of pulmonary alveoli but not high enough to lead to their excessive inflation [2, 9, 11]. When a given group of alveoli collapses, the traction force exerted on their walls by the adjacent relaxed units multiplies due to the so-called parenchymal (interstitial) interdependence, which results primarily from the route of connective tissue fibres in the lung structure (connective tissue syncytium) [5, 10, 15]. Although these forces favour re-aeration of atelectatic units, they may reach values that cause substantial local stress at the link between the collapsed and relaxed pulmonary zones. Using a theoretical, mathematical model already in the 1970s, we estimated that the transpulmonary gradient of 30 cm H_2O (2.9 kPa) might result in the local pressure of 140 cm H_2O (13.7 kPa) [2, 5, 6, 16] at the border of the phases mentioned.

We assumed that alternate opening and collapsing of lung units may generate damaging traverse forces usually localised in the dependent parts of the lungs, which in turn leads to the development of emphysematous alveoli or pseudocysts. We stress that these morphological changes (often found in the perihilar regions) are not influenced by excessive inflation of the alveoli, which usually occurs in the independent regions of the lungs [11, 15]. When the collapsed units suddenly open and recollapse, the traverse forces may be sufficiently potent to damage the airway epithelium, critically stress the system of pulmonary capillaries and cause surfactant dysfunction, ultimately initiating an inflammatory reaction [15]. The existence of zones of different time constants and biomechanical heterogeneity of lungs are enhanced by airway changes. In addition to the parenchymal dependence multiplying stresses at the borders of opened and collapsed units, small-diameter airways surrounded by consolidated airless parenchyma are strained by the high pressure of central air passages. Minor bronchioles (below generation 10–11), unprotected by cartilage scaffolding, become inflated and damaged [15].

Another important factor that contributes to lung injury at various stages of their pathology is oxidative stress. The pathomechanism of this reaction most likely involves the increased formation of oxygen radicals and the enhancement of apoptosis of pulmonary structural cells. Hence, a widely known strategy, applied also in the ARDS therapy, uses minimum possible oxygen concentrations that ensure $SaO_2 \geq 90\%$ [5, 13].

PULMONARY OEDEMA IN THE COURSE OF VILI/VALI

First described by Webb and Tierney [17], pulmonary oedema, which is the most frequently described symptom accompanying both VILI and VALI, is caused by ventilation with high airway pressures (with high transpulmonary pressure) of previously healthy lungs. The lungs of rats subjected to ventilation with peak pressure of 45 cm H_2O (4.4 kPa) and PEEP showed considerable injury already after 20 minutes (oedema, alveolar haemorrhage), whereas lungs ventilated with peak pressure of 45 cm H_2O (4.4 kPa) and PEEP 10 cm H_2O (0.98 kPa) were significantly less damaged. It has been almost 40 years since scientists pondered over the possible beneficial role of PEEP as an element for alleviating the harmful effects of ventilation.

The vascular component of the development of oedema during mechanical ventilation is double. First, it has been demonstrated that during lung inflation, the pressure in the interstitium around the extra-alveolar blood vessels decreases (due to parenchymal interdependence). Simultaneously, the transmural pressure in these vessels increases, which favours their dilation. A completely different phenomenon concerns the vessels in direct contact with the alveolar walls. During inflation of a normally aerated lung, the majority of capillaries integrally connected with the alveolar basement membrane are compressed because of increased volume of the alveolus, which causes the decrease in surfactant layer thickness and its inactivation, proportionally to the V_T value and inflation duration [2, 18]. Such an image, characteristic of mechanical ventilation with positive pressures, triggers the increase in filtration pressure in both types of pulmonary capillaries, which creates the conditions suitable for the

development of oedema [1, 2, 17]. Second, the permeability of the alveolar capillary barrier increases, which seems more important in the described mechanism of pulmonary oedema occurrence. The process was found during experimental ventilation with high V_T of undamaged lungs, as well as in the initial, exudative phase of ARDS (VALI and VASI, ventilator-associated systemic inflammation). Oedema fluid is protein-rich, which confirms the increased permeability of the epithelium and the endothelial microcirculation barrier [1, 2, 19, 20]. Initially, changes involve the endothelium, are detectable under electron microscope and appear to precede changes in the alveolar epithelium. Endothelial cells separate focally from their basement membranes and form intracapillary alveoli, which eventually lead to open, diffuse injury to alveoli whose epithelial surface breaks. In this process, type I sealing pneumocytes undergo greater destruction than type II lamellar pneumocytes, which are responsible for resorption and surfactant synthesis. This phenomenon is essential for the mechanism of VILI/VALI development. Disorders in the composition of or the actual deficiency of surfactant alter the pulmonary alveolar response to increased surface tension. Consequently, alveoli and minor airways (below generation 16) tend to collapse and generate tangential forces during reopening. The resultant heterogeneous distribution of tidal volume to individual lung units increases regional stretching by the phenomenon of interdependence, which also increases the vascular filtration pressure, favouring the development of oedema [1, 2]. Histopathologically, visible broadened bronchioles in the consolidated areas are also observed [1, 2, 5]. Lungs that were originally damaged by a disease (e.g., pneumonia) and subjected to mechanical ventilation are more susceptible to its detrimental effects (VASI). Moreover, various lung reactions to mechanical ventilation in cases of their acute injury both of pulmonary or non-pulmonary origin cannot be excluded [21].

MODULATING THE COURSE OF VILI/VALI

The basic factor affecting the course of VALI is the use of low tidal volumes within a broader strategy of protective ventilation. Many experimental studies that focused on methods for alleviating the course and consequences of VALI, using certain pharmacological agents, failed to bring explicit results. Therefore, the ideas and concepts presented in this study are of a hypothetical nature. They consider the measures to decrease the harmful effects of ventilation on the lungs and to modulate cellular mechanotransduction. In this respect, pharmaceutical agents could become an attractive addition to lung-protective ventilation. A good example would be studies on the effectiveness of renin-angiotensin system inhibition in the alleviation of VILI by reducing the release of proinflammatory cytokines and the blocking of apoptosis [20, 22, 23]. Angiotensin II triggers lung injury induced by acid aspiration, or in the course of severe sepsis, because its level increases locally in the VILI-affected lung. VILI can also be pharmacologically modulated with ionic channel blockers (gadolinium), β_2-adrenomimetic drugs (terbutaline) and adrenomedullin to reduce the permeability of the alveolar capillary barrier [24–26]. Similar inhibitory effects on the permeability of pulmonary capillaries in VILI were also shown for metformin [27].

To date, none of the listed agents has been demonstrated to be useful in the treatment of humans; considering the complexity of VILI/VALI mechanism, it seems highly unlikely that single pharmacological interventions could be clinically effective. However, the lung-protective strategy previously mentioned proves its clinical usefulness by influencing the basic VILI/VALI factors. It reduces the repetitive, excessive strain of alveoli, development of traverse forces, oedema, inflammatory response, apoptosis and formation of radicals [7, 12, 28]. This strategy is not, however, free of practical problems. The use of low V_T often leads to hypercarbia (hypercapnia) and hypercapnic acidosis (HCA). Both phenomena may also be considered an element of lung protection. According to several opinions, acidosis itself associated with the excess of CO_2 modulates biotrauma, thereby reducing the release of proinflammatory mediators from alveolar macrophages and limiting the formation of immune response cell infiltrations in the lungs [29–32]. In the animal study (mice) with experimentally induced VILI, hypercapnia inhibited transcription and translation of the primary inducible enzyme of COX-2 formation [29]. Unfortunately, it coincided with increased levels of 3-nitrotyrosine in the lungs, which is an indicator of cellular oxidative stress (similar to the one observed in severe sepsis).

Taking into account the potentially alleviating effect of hypercapnic acidosis (the side effect of V_T reduction in ARDS) on VILI/VALI, several scientists consider the likelihood of changing the term "permissive" hypercapnia to "therapeutic" hypercapnia. The latter may be achieved not only by a decrease in V_T but also by the intended addition of CO_2 to the respiratory mixture in the concentration of 5–15% [32, 33]. Other benefits derived from HCA include improvement of lung compliance by increased surfactant secretion (the effect stimulated by pH reduction) or decrease in permeability of pulmonary capillary bed [30, 34]. The drawbacks of HCA include increased pressure in the pulmonary artery in patients with ARDS and possible impaired contraction of the right ventricle [35, 36, 37]. Moreover, debilitating and delaying effects of HCA on the repair of lung epithelial injuries dependent on the inhibition of NF-κB activation (changes in the activity of metalloproteinases in the cytoplasm) are discussed [31, 34, 38]. The experimental data regarding HCA suggest that the direct and indirect protective effects of HCA

depend on the time-dependent pH reduction (not the increase in $PaCO_2$) as a lung injury preventative factor. Reduced formation of inflammatory mediators, inhibited formation of oxygen and nitrogen radicals by affecting xanthine oxidase and improved surfactant activity seem to evidence the likely positive role of HCA in lung injury prevention. Moreover, it should be stressed that clinical applications include now the possibility of $PaCO_2$ and HCA control during the use of very low values of V_T (super-protective ventilation) via its extracorporeal elimination. This strategy and possible impact of "super-protective ventilation" on VALI are currently being clinically evaluated [2, 12, 30, 31]. The influence of HCA on cerebral circulation is commonly known and its description is beyond the scope of this paper.

PRACTICAL IMPLICATIONS OF THE KNOWLEDGE OF VILI/VALI PATHOLOGY

The chief practical applications of the knowledge of VILI and VALI pathomechanisms include the reduction of tidal volumes and inhibition of atelectrauma. V_T reduction limits the end-expiratory tidal volume, which hinders the lung stress and strain [9, 12]. Plateau pressure helps to estimate the end-expiratory tidal volume; however, transpulmonary pressure plays a key role in the evaluation of excessive oedema [10, 28]. Reduction of atelectrauma effects is connected with the optimisation of PEEP values. The adequate PEEP level, however, remains a subject of dispute. Randomised, multicentre, clinical trials and meta-analyses failed to confirm that PEEP higher than 12 cm H_2O (1.2 kPa) reduces the mortality of patients with ARDS [39–42]. The beneficial effects of increased PEEP in ARDS patients with the most severe hypoxemia are noteworthy [39]. A new, "Berlin" definition of ARDS describes this subgroup as severe ARDS ($PaO_2/F_IO_2 \leq 100$ mm Hg (13.3 kPa) with PEEP ≥ 5 cm H_2O (0.5 kPa). This definition, as well as current reports on the subject, may suggest that a lack of explicit evaluation of PEEP could result from the fact that previous studies were based on patients with ALI and ARDS, most likely two separate conditions of different pathophysiology. New studies on the influence of PEEP on the course of ARDS, defined in accordance with current guidelines, will be required [43]. Nevertheless, regardless of the results, PEEP and other parameters should be "tailored" (Gattinoni L) for each patient, based on individual, accurate indices of biochemical lung evaluation [10, 12].

It should also be borne in mind that with several types of severe ARDS, a safe strategy does not exist because of critical heterogeneity of pulmonary parenchyma, and choosing a lesser evil must account for the character of dominant biomechanical changes. To minimise the losses within the lungs, a well-known rule of positioning ventilation should be applied, namely, "good lung down" or prone position. The influence of this practice on the final success of ventilatory treatment has not been confirmed; however, immediate improvement of ventilatory conditions (gasometric parameters) is an unquestionable element of such management [12, 28].

Furthermore, the issue of mechanical ventilation of initially uninjured lungs in a subset of ICU patients (e.g., those with neuromuscular diseases) and during general anaesthesia, especially for long surgical procedures, is essential. The biomechanics of lungs with ARDS and "healthy" lungs is completely different; therefore, ventilatory strategies for initially injured lungs may seem inappropriate for patients with healthy lungs. The opinions vary on this issue, and animal studies have produced surprising results. Reduced biotrauma features were observed (cytokine level in BAL, initially healthy lung) in the groups with lower PEEP (respectively VT = 15 mL/3 cm H_2O [0,3 kPa] PEEP and VT = 6 mL/3 cm H_2O [0,3 kPa] PEEP) after 8 hours of ventilation, compared to the group with low V_T and higher PEEP (V_T = 6 mL/PEEP = 10 cm H_2O [0.98 kPa]) [44]. Similar conclusions were reached during intra-operative observations. We observed that the injury features increased in the group ventilated in accordance with lung-protective ventilation [2, 10, 44–46]. Nonetheless, several randomised, prospective studies published recently stressed the prophylactic nature of protective ventilation [2, 45, 47, 48, 49], For instance, the study by Serpa Neto and colleagues [50] included 2,822 patients without lung pathology, who were subjected to protective mechanical ventilation. A reduced incidence of VILI considerably decreased mortality. Similar conclusions were reached by Imberger and co-workers [51]; the protective application of PEEP during intraoperative lung ventilation increased the postoperative values of PaO_2/F_IO_2 and reduced atelectatic areas (evaluated tomographically). In this case, however, the post-operative mortality did not decrease.

OTHER STRATEGIES OF INJURED LUNG PROTECTION

Apart from the conventional mechanical ventilation, a number of other strategies are being considered, which may prove to be valuable because our knowledge of VILI and VALI pathophysiology is expanding. The alternative procedures include high-frequency oscillation (HFO) that may ensure full and continuous lung recruitment at very low V_T and controlled high P_{aw}. Because of a limited number and the homogeneity of studies on adult patients, we can only confirm that HFO considerably improves oxygenation, without a noticeable impact on the development of VALI and the mortality of patients with ARDS who are subjected to artificial ventilation. For this reason, additional large, prospective studies have been conducted to compare HFO with conventional ventilation and low V_T in patients with ARDS (OSCILLATE TRIAL, Canada; OSCAR, Great Britain) [12, 50].

Another strategy for efficient pulmonary ventilation in patients with severe lung injury and minimisation of VALI is extracorporeal membrane oxygenation (ECMO), which is based on the concept of "resting" of injured lungs. The recent AH1N1 flu pandemic showed higher survival rates of patients who had viral lung injury and were treated with ECMO. Gattinoni and colleagues suggested the verification of current recommendations and earlier application of ECMO in cases of complex lung pathology of various aetiology [12, 52, 53].

Another large study on VALI prevention focused on the benefits of early (limited to 48 hours) administration of agents that blocked the neuromuscular junction. Obviously, greater ventilatory comfort in the studied population was related to lowered transpulmonary pressure and decreased 28-day mortality [54].

Various forms of exogenous surfactant supply in adults with ARDS did not bring satisfactory results. Laboratory evaluation of partial fluid ventilation with the use of perfluorocarbons was equally disappointing. Similarly, studies on VILI prevention with large solution volumes (20–30 mL kg^{-1}) as well as smaller ones (3–10 mL kg^{-1}) have failed to bring encouraging results. The process impairs lung biomechanics and consequently increases the mortality in experimental animals [50].

The last of the analysed methods for VILI/VALI prevention uses the spontaneous activity of respiratory centre and natural alterations in tidal volume and respiratory rate (noisy ventilation). This strategy of lung ventilation, often superimposed on one of the systems of ventilation with reduced pressure and significantly different from standard rules of protective ventilation, brought about surprisingly good outcomes in several experimental and clinical studies. Improvement in biomechanical indices, including the reduction of atelectrauma, is an unexpected result; however, the process requires a broader strategy and more intensive, in-depth assessment [50, 55].

To conclude, following the *primum non nocere* rule during mechanical ventilation is a complex and multidirectional process, which requires more advanced devices and continuous training of physicians. Under such conditions, the doctrine is not always attainable or feasible, although the progress that has been made can be considered to be a practical success of "applied physiology" [50]. Nevertheless, the tools for preventing primary lung injury and limiting secondary deterioration of lung function during ventilation are, in many cases, controversial, which served as the motivating factor for this study. Currently, it seems that low tidal volumes and adequate end-expiratory pressures (set using the available methods) are the best understood and documented measures for lung protective ventilation during ventilatory therapy and likely during the ventilation of unaffected lungs.

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Received: 6.12.2012
Accepted: 22.06.2013