Ventilator induced lung injury

JJ Spijkstra1, H Biermann2, DG Markhorst2
1Department of Intensive Care and
2Department of Paediatric Intensive Care
Vrije Universiteit Medical Center, Amsterdam, The Netherlands

Introduction
As early as 30 years ago it was recognized that mechanical ventilation in healthy animals could cause lung abnormalities very similar to the Acute Respiratory Distress Syndrome (ARDS). In subsequent years it has become apparent that the damage was caused by ventilation with high inspiratory pressures, or rather high tidal volumes, causing overdistention. In addition to this it became known that the cyclical opening and closing of alveoli during mechanical ventilation, called shear-stress, could be harmful to the lungs. This newly gained knowledge led to the understanding that, although necessary and often life saving, mechanical ventilation could lead to additional damage to the lungs in patients with respiratory insufficiency. At first the damage was thought to be local and restricted to the lungs, however evidence is growing that mechanical ventilation may actually lead to systemic damage and multiple organ failure (MOF). Based on these concepts new strategies of mechanical ventilation were developed and tried, which, in part, proved to be successful. In this review we will focus on the various mechanisms which cause damage to the lungs and consequently may lead to MOF, while we will briefly address the practical implications of this knowledge for ventilatory strategies.

From barotrauma to volutrauma
For years damage to the lungs associated with mechanical ventilation, commonly referred to as Ventilator Induced Lung Injury (VILI), with clinical signs of subcutaneous emphysema and pneumothorax, was thought to be caused by high inflation pressures, inducing alveolar rupture and air-leaks, and was therefore called barotrauma. As recently as 15 years ago, pneumothorax was seen in 60% of patients treated for ARDS. Over the years this figure has gradually declined to below 10% (2), and in a recent study pneumothorax was only found in 6.5% of cases of ARDS and in 2.5% of patients ventilated for all causes including ARDS (3). These declining numbers indicate that clinicians have learned from their earlier mistakes and that mechanical ventilation is safer than it used to be as, over the years, we have learned that the damage was derived from the fact that ventilation with high pressures caused by ventilation with high tidal volumes and was not related to either low or high ventilation pressures (Fig.1) (6). Moreover, damage could even be provoked by negative pressure ventilation (7). Further proof that high pressures are in themselves not responsible for lung damage was derived from the fact that ventilation with high pressures in animals in which the thoracic walls were restricted did not lead to pulmonary damage. In these experiments thoracic wall excursion was partially prevented by plaster casts, and high ventilation pressures were thus necessary to induce normal tidal volume (7,8).

Over the years this phenomenon from barotrauma to volutrauma.

These findings were from animals with previously healthy lungs. Of course most ventilated patients have diseased lungs, and this has prompted researchers to assess whether mechanical ventilation has the same effects in isolated diseased lungs, or in animals in which ARDS had been induced, normally by lavage of the lungs with saline or by injuring the lungs with oleic acid. In isolated rabbit lungs, neither low doses of oleic acid alone, nor ventilation with low tidal volumes will lead to damage of the lungs. However, if the two are combined the same dose of oleic acid is followed by ventilation with the same tidal volumes this does result in an increase in capillary leakage and oedema formation (9). Likewise observations can be made in ventilated rats with or without injured lungs. In rats with injured lungs, pulmonary damage, defined as capillary leakage and pulmonary oedema, is seen at smaller tidal volumes than in ventilated rats with normal lungs. If damage does occur, then at the same tidal volume more damage is seen in injured lungs than in normal lungs (10). However, if the two are combined and the same dose of oleic acid is followed by ventilation with the same tidal volumes this does result in an increase in capillary leakage and oedema formation (10). Likewise observations can be made in ventilated rats with or without injured lungs. In rats with injured lungs, pulmonary damage, defined as capillary leakage and pulmonary oedema, is seen at smaller tidal volumes than in ventilated rats with normal lungs. If damage does occur, then at the same tidal volume more damage is seen in injured lungs than in normal lungs (10). In fact diseased lungs can be very sensitive to volutrauma and may show signs of increased damage to even very small insults, as for instance in prolonged anaesthesia for surgery. The level of sensitivity is likely to be related to the amount of damage in the lungs before ventilation. The more extensive the pulmonary abnormalities, the more susceptible the lungs to damage from the ventilator. The increased susceptibility of diseased lungs to ventilation injury can be explained by the uneven distribution of the alveolar abnormalities in ARDS. As demonstrated by CT-scans of ARDS patients, atelectatic and flooded areas of the lungs caused by capillary leakage and bleeding as well as damage to the lung

Correspondence
JJ Spijkstra
E-mail: jj.spijkstra@vumc.nl
tissue, are mostly situated in the dependent parts of the lungs. In the non-dependent parts, the lung tissue may be relatively or completely normal (12). A tidal volume delivered by the ventilator will follow the direction of least resistance and inflate the non-dependent lung areas, whereas the dependent, collapsed areas won’t be inflated at all. A “normal” tidal volume that otherwise would not have been deleterious to a normal lung, will thus be delivered to only a small portion of the lung an may cause regional overdistention and volutrauma. In 1987Gattinoni suggested that this mechanism of ventilation with its relatively high tidal volumes to the available lung tissue as an explanation for ventilator induced injury in ARDS patients and called this concept ventilation of the “baby lung” (13).

**Atelectrauma or shear-stress**

In the experiments in which the damaging effects of high tidal volume ventilation were established, it was also noticed that these damaging effects could be attenuated by the application of PEEP (Fig.2) (5,7). Although at that time the protective effects of PEEP were not fully understood, the explanation for this phenomenon had already been given years before these effects were noticed. In 1970 Mead and colleagues proposed a model of the lung in which the alveoli are interdependent and the alveolar walls mutually supportive. If an alveolus collapses this gives rise to strains on the neighbouring walls that are much greater than in the normal situation in which all alveoli are equally inflated (14). In a situation in which parts of the lungs collapse and are cyclically re-opened this would lead to great disrupting forces in the border zones between open and cyclically closed parts of the lungs (Fig. 3). This phenomenon, which has been called shear-stress, could than be attenuated by PEEP by preventing the lung from collapsing. This concept was first proposed as an explanation for the lung damage seen in infants with respiratory distress syndrome (15) and for the decrease in lung injury observed when high-frequency ventilation was applied in an animal model of ARDS with mean airway pressures high enough to prevent the lungs from collapsing (16). Under normal conditions the lungs are kept open by negative intra-pleural pressure and the pull of the respiratory muscles. If these forces diminish, as is the case during anaesthesia with sedation, neuromuscular blockade and mechanical ventilation, the gravitational dependent portions of the lungs may collapse (17). The same may be true of ARDS lungs in which the volume of the extra-vascular lung water increases. This, in turn increases the lung weight and causes the airways and lung parenchyma to collapse, mainly in the gravitational dependant lung regions (18,19). Thus in disease states as well as during medical procedures, extensive areas of the lungs are prone to collapse and to develop shear-stress. Although the concept of shear-stress has been one of the leading principles of the hypothesis on the development of ventilator induced lung injury, it has been very difficult to establish its existence beyond doubt. There are now several lines of evidence to suggest the importance of this mechanism. Firstly it has been shown in in vitro studies that repetitive stretching of alveolar epithelial cells is more damaging than tonically held deformation. Moreover, damage from cyclical large-amplitude deformation could be diminished by reducing relaxation by increasing the tonic expansion (20). Secondly, although PEEP was found to provide some degree, of protection against the deleterious effects of high volume ventilation in the original animal experiments (5,7), it was difficult to ascribe all the protective effects to PEEP per se, because the oxygenation and perfusion of the lungs differed between the groups and these could theoretically, in part, be responsible for the damage reduction. Therefore new experiments were performed in isolated and lavaged rat lungs, in which the possible confounding effects of oxygenation and lung perfusion were eliminated. It was found that either low (21) or high (22) tidal volume ventilation without PEEP aggravated the previous lung damage, whereas this could be attenuated by preventing the collapse of the lungs at expiration with enough PEEP. In the PEEP groups, cytokines in BAL fluids were significantly lower thus indicating less inflammation and cell damage (22). Thirdly, the existence and importance of shear-stress is also supported by experiments with High Frequency Oscillatory Ventilation (HFOV). In HFOV the lungs are kept inflated with high expiratory lung volume. In rabbit lung-lavage models it was possible to keep the animals alive, with a persistent high PO2, with HFOV, while in a comparison group using conventional ventilation with low PEEP, all animals showed a deterioration in oxygenation and finally died (23). Another rabbit experiment showed that these results were not produced by HFOV per se. This experiment in which conventional ventilation with a strategy to fully open the lungs and keep the lungs open with enough PEEP, produced the same results as HFOV with the same expiratory lung volume (24). Perhaps the most convincing evidence for the role of shear-stress in the development of VILI has recently been given in a series of

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**Figure 1.** Extravascular lung water (Qwl), dry lung weight (DLW) and albumin space (Alb.Sp.) as a measure of capillary leakage and inflammation activity in rats ventilated with high airway pressure and high tidal volume (HiP-HiV), low pressure and high volume (LoP-HiV) and high pressure and low volume (HiP-LoV). Horizontal dotted lines represent the upper 95% confidence limit for control values. PEEP protects from the deleterious effects of high volume ventilation. (From Reference 7, with permission)

**Figure 2.** Extravascular lung water (Qwl), dry lung weight (DLW) and albumin space (Alb.Sp.) in rats ventilated with high airway pressure and high tidal volume at zero end expiratory pressure (HiP-HiV) and with 10 cm H2O PEEP. Horizontal dotted lines represent the upper 95% confidence limit for control values. PEEP protects from the deleterious effects of high volume ventilation. (From Reference 7, with permission)
Mechanical strain on lung cells will result in the release of mediators, both in vitro and in vivo. The cells involved may be alveolar epithelial cells, but also macrophages, fibroblasts or even smooth muscle cells (29). The strain will also lead to direct damage to the cells with disruption of the cell membrane and of the alveolo-capillary membrane resulting in an increase in permeability and leading to interstitial and alveolar oedema. Disruption of the endothelial cell layer leads to an infiltration of inflammatory cells into the interstitial and alveolar spaces. These activated inflammatory cells will add to the cytokine release (30). Under normal circumstances locally produced cytokines are confined within the alveolar barrier, however disruption of this barrier would make it possible for the cytokines to enter the circulation (31). In the same way, also bacteria can leak from within the lung into the bloodstream (32). These findings have been confirmed in animal experiments. Injurious ventilatory strategies in rats led to an increase of pro-inflammatory cytokines in serum as well as in BAL fluids (33,34). Although at this time, not all questions have been fully answered it is very likely that these cytokines are indeed an essential part of the driving force in the development of MOF (35,36). In agreement with this, Raineri found a decrease in the extent of MOF in a group of ARDS patients ventilated with a lung protective strategy (37). Similar results were obtained in another study comparing lung protective ventilation with conventional ventilation, in which a post-study analysis showed a decrease in MOF as a result of by lung protective ventilation (38).

Clinical implications

The growing awareness that mechanical ventilation can be deleterious both to diseased lungs as well as to the body, and the accumulated knowledge of the mechanisms involved have led to the development of ventilation strategies to prevent this damage. The possible damage to the lungs inflicted by ventilation with high tidal volumes was assessed in a multi-centre, randomized trial in ARDS patients in the United States, in which ventilation with low tidal volumes (6 cc/kg ideal body weight [ibw]) was compared with a control group ventilated with “normal “ tidal volumes (12 cc/kg ibw). A clear reduction in mortality was found in the low tidal volume group, supporting the concept of volutrauma (38). The meaning of this finding has been intensively discussed. The main criticism focused on the control group, ventilated with tidal volumes of 12 cc / kg ibw, which were considered larger than normal, thus inducing more mortality in the control group than would have been the case under normal conditions (39). However analysis of the original data, as well as data from a survey of ventilation habits in ICUs in 20 countries spread over three continents, showed that tidal volumes of 12 cc / kg ibw are quite common in ARDS patients (40,41), and these results are now widely accepted. Moreover, in a recently published prospective study, the mortality reduction seen in small tidal volumes was confirmed (42). It is less clear whether ventilated patients...
without ARDS or ALI are susceptible to volutrauma to the same degree. A retrospective study in patients ventilated for longer periods of time for reasons other than ALI, showed that ventilation with high or very high, tidal volumes induces ALI in a high percentage of patients (43), however this finding has not been corroborated and it has been argued that ALI only develop in patients with a preset condition such as a primary inflammatory stimulus, which makes them especially vulnerable to develop ALI (44). Nevertheless, it is now recommended that clinicians should be cautious when using high tidal volumes in patients without ALI or ARDS, and that small tidal volumes should be the gold standard ventilatory treatment for patients with ARDS (45).

The importance of shear-stress was addressed in another large randomized controlled trial in which ARDS patients were ventilated with low tidal volumes and in addition received either low or higher levels of PEEP. Higher PEEP levels did not decrease morbidity or mortality, and the trial was stopped before its scheduled end because of lack of difference between the study groups (46). Unfortunately the PEEP for the patients in this study was determined by a PEEP/FiO$_2$ table and not based on the individual patient’s lung mechanics. The importance of this was shown in a study in 19 ARDS patients, in which both the lower and the higher PEEP strategy was successively used in all patients. In only half the patients did the high PEEP strategy result in significant alveolar recruitment i.e. the opening of closed parts of the lungs, whereas this recruitment was minimal in the other half (47).

In a randomized controlled trial to evaluate lung protective strategies, Villar and co workers combined smaller tidal volumes with PEEP levels high enough to keep the lungs open. The PEEP levels of each patient were assessed by performing a pressure volume curve test, and thus the individual lung mechanics were used to find the optimal ventilator settings. This study resulted in a significant reduction in mortality, even though the groups were comparatively small and the difference in tidal volumes between the groups studied were smaller than in the American study (Fig. 5) (42). Although the effects of higher PEEP levels alone were not assessed, these results are nevertheless very suggestive of the synergistic effect of higher PEEP levels, protecting against atelectrauma, and thus increasing the overall lung protective effect of a low tidal volume strategy.

A lot of questions are still waiting for an answer; how low should the tidal-volumes actually be to obtain the best results? Is shear-stress a relevant clinical problem or not, and if so, how should it be dealt with? Is it possible to interfere with the actions of cytokines released during ventilation? etc.

In the meanwhile much can be gained by simply using ventilation strategies already proven to be beneficial such as lowering the tidal volumes. This is, however, not as likely to happen as it should be; both a national and an international survey have shown that many patients are still being ventilated at tidal volumes greater than the recommended 6 cc/kg (49,50). In conclusion, given the available evidence, patients with ALI or ARDS should not be ventilated with tidal volumes greater than 6 or 7 cc/kg pbw, and this is probably also the best strategy for those patients ventilated for other reasons. Although the use of higher levels of PEEP is still being debated, there is, in our opinion, enough evidence to suggest that this is indeed beneficial, provided the ventilator is set in accordance with the physiological properties of the individual patient, while the same is probably true for recruitment of the lungs.

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