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INTRODUCTION

Since its first description more than 25 years ago [1], the acute respiratory distress syndrome (ARDS) has received more attention than any other single entity in critical care medicine. The syndrome consists of an acute, severe alteration in lung structure and function characterized by severe hypoxemia, low respiratory system compliance, low functional residual capacity and diffuse radiographic infiltrates, along with increased lung endothelial and alveolar epithelial permeability.

Thus intrapulmonary shunt and ventilation-perfusion imbalances cause life threatening hypoxemia. Moreover, high work of breathing from increased dead space and reduced respiratory compliance may cause further ventilatory failure. The main supportive care of ARDS is the mechanical ventilation. By stabilizing respiration, mechanical ventilation allows to gain time for administration of treatment for the underlying cause of ARDS (antibiotic or surgical) and for the evolution of the natural healing process. On the other hand it has been recognized that mechanical ventilation per se can be injurious to the lung due to excessive pressure-volume, excessive opening and collapses forces and potentially self-inducing inflammation to the lung. Arterial oxygenation can be supported by different methods, but it is not yet completely clear which of them are joined with less ventilator-associated lung injury. These strategies can be briefly summarized as "mechanical strategies" involving the ventilatory setting or "pharmacological strategies" involving administration of drugs to potentially improve oxygenation. These strategies can be different in the early compared to the late stages of ARDS, due to the important morphological changes occurring with the progression of the disease.

LUNG STRUCTURE IN ACUTE RESPIRATORY DISTRESS SYNDROME IN THE EARLY PHASE

Lung injury may be caused by a direct insult on the lung ("direct insult"), or by pulmonary lesions that result from an acute systemic inflammatory response ("indirect insult"). In the direct insult pulmonary epithelium is subjected to an initial injury, with activation of alveolar macrophages and the inflammatory network, which leads to pulmonary inflammation. In the indirect insult the pulmonary lesions may also originate from extrapulmonary foci into the blood, as during peritonitis, pancreatitis and various abdominal diseases. The subsequent lesions of the alveolar-endothelial barrier cause an increase in the vascular permeability with an increased interstitial and alveolar edema. The distribution of edema is quite uniform throughout the lung parenchyma, suggesting that the vascular permeability defect should also be evenly distributed [2]. As the total mass of a ARDS lung is more than twice that of a normal lung, the lung progressively collapses under its own weight. The ARDS lung is uniformly affected by the primary disease, and edema accumulates uniformly, as a sponge immersed in the water. The gas spaces are restricted by edema and the total gas content decreases. The increased hydrostatic forces progressively compress the lung regions along the vertical axis, and the gas is progressively squeezed out from the dependent regions, with formation of compression atelectasis.

This is why ARDS is characterized by radiographic densities, primarily located in the dependent regions, namely the vertebral ones in supine position [3]. Using CT analysis of the regional expiratory limb of the PV curve, we found that the upper lung regions are always open, while the middle and lower lung regions present a progressive higher closing pressure [4].

Other mechanisms than the superimposed pressure due to the gravitational forces in an edematous "heavy" lung [5] have been found to be responsible for the presence of atelectasis in the dependent lung such as 1) the weight of the heart [6,7], 2) the possible increase in the abdominal pressure [8], 3) the possible deficit of surfactant [9].

Thus, the ARDS lung is composed of normally inflated lung regions, consolidated lung regions and collapsed-atelectatic-recruitable lung regions.

The normally inflated lung regions are primarily distributed in the non-dependent lung regions. The collapsed-atelectatic lung regions are distributed along the vertical gradient from non-dependent to dependent

lung, and the extent likely depends of the severity of the disease and edema formation, the shape of the thoracic cage, and the shape of the heart. Finally, the consolidated lung regions are evenly distributed throughout the lung parenchyma. Both the atelectatic and consolidated lung regions represent, if perfused, the main cause of hypoxemia and pulmonary shunt. However, it is noteworthy that in ARDS, despite the generalized vasoconstriction, collapsed lung regions are appropriately underperfused compared with the inflated regions.

EFFECTS OF TIDAL VOLUME AND PEEP ON LUNG STRUCTURE

During mechanical ventilation and tidal volume breathing, a considerable part of the lung continuously collapses and decollapses, especially if PEEP is not enough high to keep the lung open at end expiration. This phenomenon occurs often in the most dependent lung regions, where compression atelectasis is prevalent. With higher PEEP levels, the reopening-collapsing tissue is decreased because the amount of collapsed tissue at end-expiration is reduced. The mechanisms underlying the effectiveness of PEEP in early ARDS relate to the presence of compression atelectasis formed under the action of hydrostatic forces. It follows that to prevent the collapse of a given pulmonary unit PEEP must be at least equal or higher than the hydrostatic forces acting over that unit. As the hydrostatic forces increase along the ventral-dorsal axis in supine position, the ideal PEEP should also increase along the same axis [5,10,11]. Consequently, the ideal PEEP to keep open the most dependent lung regions is excessive in the non-dependent lung, where overdistension occurs [4].

EFFECTS OF RECRUITMENT ON LUNG STRUCTURE

From the law of La Place we know that a critical opening pressure has to be overcome before the lung volume is augmented, the prerequisite for the recruitment and stabilization of collapsed lung areas. Therefore, the goal of an inspiratory pressure increase is to determine this critical opening pressure. Several factors determine the elevated pressure needed to open up previously collapsed alveoli: 1) the absence or reduction in surfactant [12]; 2) the reduced size of the alveoli to be reopened [5]; 3) the increased regional pleural pressure gradient in the most dependent part of the lung, i.e. a lower transpulmonary pressure at the same alveolar pressure [13]; 4) the weight of the heart on the most dependent part of the lung [6,14]; 5) the reduction in chest wall compliance, often due to an increase in the intraabdominal pressure [15,16,17]. Thus the transmural pressure required to open atelectasis in supine position may be high even at 30-35 cmH₂O (*i.e.* 50-60 cmH₂O in the respiratory system in particular conditions).

Several approaches have been used to perform recruitment maneuver as the applications of continuous positive airway pressure of 35-40 cmH₂O for 40 seconds [18], intermittent higher tidal volumes [19], intermittent higher PEEP [20], extended sigh [21].

In our opinion, the adequate recruitment maneuver depends on the patient's characteristic and a few rules should be observed. First, we should consider that the "potential" for recruitment is low in primary ARDS and large in secondary ARDS [17]. Second, it must be kept in mind that the actual opening pressure is the transpulmonary pressure, which strictly depends on the elastances of the lung and chest wall.

In fact, $TP = Paw * [EL / (EL + EW)]$, in which TP is the transpulmonary pressure, Paw is the applied airway pressure, EL is the elastance of the lung and EW is the elastance of the chest wall. In normal condition EL equals EW and the TP would be approximately 50% of the applied pressure to the airways. In primary ARDS, EL is greater than EW while in secondary ARDS is the opposite [17]. It follows that, to reach the same transpulmonary pressure, a higher Paw is necessary in secondary ARDS. Indeed for the same applied airway pressure the potential risk of the recruitment maneuver would be barotrauma in primary ARDS (high transpulmonary pressure) and hemodynamic derangement in secondary ARDS (high pleural pressure).

MECHANICAL DETERMINANTS OF LUNG INJURY

HIGH PRESSURE- HIGH VOLUME (BAROTRAUMA-VOLOTRAUMA)

Barotrauma has been attributed to mean airway pressure, peak pressure or PEEP. High airway pressure was first considered as the major determinant of lung injury, causing the passage of alveolar air to the extraalveolar space [22]. A number of animal [23,24,25,26] and human studies [27,28] documented a high association between the incidence of barotrauma and high inspiratory peak pressures. The caused damage was called barotrauma, which includes: interstitial emphysema [29], pneumomediastinum [29], pneumothorax [22], and gas embolism [26]. In the late stages of ALI/ARDS the use of high airway pressure treatment was associated with the appearance of emphysema like lesions [30,31,32,33].

However, the concept of barotrauma was challenged by Dreyfuss et al. who underlined the importance of high volumes (*i.e.*, volotrauma) instead of high pressures to induce lung injury. Pressure alone may be an important risk factor only to the extent that it reflects or influences the transalveolar pressure and thus the alveolar distension [34,35,25]. In an animal model, high tidal volume caused severe lung edema, not observed in animals ventilated with the same high airway pressure but lower tidal volume. Previous work also showed that the use of high volumes caused an increase of lung permeability [36] and lung edema [37].

In our opinion barotrauma and volotrauma are two aspects of the same phenomenon: the abnormal increase of transpulmonary pressure, which is the distending force of the lung. The high airway pressure per se does not cause barotrauma, if the transpulmonary pressure is normal, due to an increase of chest wall elastance. In fact, in Dreyfuss experiment's the pleural pressure was likely increased by the chest wall binding [38]. On the other hand the high volume per se does not induce lung damage when the transpulmonary pressure is in normal range, as when ventilating with large tidal volume lungs with an elevated functional residual capacity.

INTRATIDAL COLLAPSE AND DECollapse (SHEAR STRESS TRAUMA, ATELECTRAUMA)

More recently several papers reported lung damages resulting from continuous collapse and decollapse of some lung regions throughout the ventilatory cycle. In fact during the inspiration most of the lung regions open up as the inspiratory pressure is sufficient to overcome the regional opening pressure. During expiration, if PEEP is inadequate, part of the lung (usually the dependent regions), undergoes collapse [11]. The damaging effect of the shear forces generated by the cycling collapse and decollapse has been theoretically quantified by Mead [39] and subsequently demonstrated in experimental [40] and clinical settings [41].

INFLAMMATORY AGENTS (BIOTRAUMA)

Besides the macroscopic effects of high volume-pressure ventilation (volotrauma-barotrauma), the injurious form of mechanical ventilation can result in inflammatory responses (*i.e.*, biotrauma) [42]. This has been shown first in an ex-vivo lung model [43] and subsequently in a in-vivo model [44]. The inflammatory mediators release may lead to distal organ damage [45,46] and predispose to the multiorgan failure [35].

However, Ricard et al. using mechanical ventilation with high tidal volume in healthy rats was unable to detect any inflammatory mediators in the lung or in the blood [47]. Similar results were obtained in patients without previous lung injury, in which high tidal volumes for one hour did not cause consistent changes of a variety of inflammatory mediators in the blood (48). Thus the role of proinflammatory cytokines in the pathogenesis of ventilator induced lung injury is still questionable (49).

REDUCED TIDAL VOLUME TO IMPROVE OXYGENATION AND TO AVOID BARO-VOLUTRAUMA

Hickling et al. first focused on the potential benefit of tidal volume reduction by disregarding of the consequent hypercapnia (*i.e.*, hypercapnia permissive), showing retrospectively a significant decrease of mortality, relatively to the expected number, in 50 ARDS patients [50]. However, hypercapnia may be a problem in intracranial pathology [51], severe pulmonary hypertension [52] and congestive heart failure [53].

In 1998, based on experts opinions, it was suggested to limit airway plateau pressure between 30-40 cmH₂O or transpulmonary pressure below 25-30 cmH₂O [54]. However, three randomized controlled trials did not find any difference in the clinical outcome comparing tidal volumes ranging from 7 to 10.7 ml/Kg [55,56,57]. However, in early 2000, the ARDS network showed a 22% decrease in mortality when ALI/ARDS patients were ventilated with 6 ml/Kg compared to 12 ml/Kg [58]. Several explanations have been proposed to explain the difference in outcome obtained in these different trials. Among them were the tidal volume differences tested, the study power, the treatment of respiratory acidosis and the presence of intrinsic PEEP. Eisner et al. in the ARDS network database found that 6 ml/Kg tidal volume ventilation was equally effective in subgroups of patients with different risk factors for ARDS [59]. Based on these results, it has been recommended that 6 ml/Kg tidal volume ventilation should be broadly applied to ARDS patients [60,61]. Its actual implementation in routine ARDS management is under investigation in the centers who participated to the study. Interestingly, it was found that patients ventilated with reduced tidal volumes showed worse oxygenation in the first week of mechanical ventilation compared to the large tidal volume group. However, after the first week a dramatic inversion was found, with patients in the reduced tidal volume group showing a rapid, marked and substantial increase in oxygenation compared to the other group. This was likely due to the delayed effect of the protective ventilation, but this effect was extremely important for determination of final outcome.

However, the mandatory use of 6 ml/Kg of tidal volume is, in our opinion, questionable. In fact while we know that 12 ml/Kg tidal volume increased mortality compared to 6 ml/Kg, we do not know the effects of the intermediate tidal volume ventilation (*i.e.*, 8-10 ml/Kg). Interestingly, in a post-hoc analysis of a randomized clinical trial in ALI/ARDS, we found that the mortality was similar at whatever tidal volume below 12 ml/Kg was used, while the mortality sharply increased with tidal volume equal or greater than 12 ml/Kg [62].

The use of an intermediate tidal volume instead of the 6 ml/Kg is not clinically irrelevant, as the 6 ml/Kg implies an increased use of sedative or muscle relaxant agents to adapt the patient to the ventilator and carries the potential of harmful effects, such as progressive atelectasis and derecruitment [63]. Indeed, in our opinion, while the mechanical ventilation with high tidal volume should be banned, the intermediate ventilation (*i.e.*, 8-10 ml/Kg of tidal volume) should be reconsidered. If in a given patient the 8-10 ml/Kg ventilation results in a transpulmonary pressure or airway pressure within the safe range, we do not see any proved reason to use the 6 ml/Kg ventilation, with its potentials complications.

PEEP TO IMPROVE OXYGENATION AND TO AVOID COLLAPSE AND DECOLLAPSE (ATELECTRAUMA-BIOTRAUMA)

Besides avoiding high volume and high pressure ventilation, the other cornerstone to improve oxygenation and to avoid ventilator associated lung injury is the application of PEEP [64]. This was stated by Lachmann [12] who focused on the concept of opening the lung (*i.e.*, recruit the lung) and keeping it open (*i.e.*, avoid the derecruitment). PEEP, in fact : 1) prevents derecruitment and maintains open previously collapsed lung regions at end-expiration, thus reducing the amount of not at all or poorly ventilated but perfused lung tissues; 2) reduces the amount of tissue continuously collapsing and decollapsing during tidal breaths, likely reducing atelectrauma and biotrauma [41].

Different methods have been proposed to select at bedside the “optimal” PEEP level. The “optimal PEEP” level is the level of PEEP at which the least part of collapsed tissue is maintained at end-expiration with the least interference with regional overdistension and hemodynamics.

PRESSURE – VOLUME CURVE

For PEEP selection the pressure-volume (PV) curve was widely used since the 70' [65,66]. The traditional view suggests that the PV curve, in its inspiratory limb, is the expression of three phenomena: 1) the lower part up to the inflection point reflects recruitment zone, 2) the straight line reflects normal inflation zone, 3) the upper inflection point reflects the overdistension zone [67]. According to this model, Amato et al. showed in a randomized clinical trial that by setting the PEEP 2 cmH₂O above the lower inflection point and limiting the airway plateau pressure to 40 cmH₂O, they had a significant increase in survival at 28 days compared to a control group [18]. Ranieri et al. using the same technique for PEEP selection, were able to decrease a variety of proinflammatory mediators in ARDS patients [41].

However, the use of inspiratory limb of the PV curve for PEEP selection appears at least questionable. Venegas, on theoretical background [68] and Hickling with a mathematical model [69,70] suggested that the recruitment occurs throughout the entire inspiratory limb of the PV curve. In computed tomography (CT) analysis of the PV curve we were not able to find differences in the recruitment across the lower inflection point [67] and more recently we found both in animal [13] and in ARDS patients [71] that recruitment is an inspiratory phenomenon occurring along the entire inspiratory limb of the PV curve, well above the lower inflection point. Indeed a bulk of data suggests that setting the PEEP (*i.e.*, controlling the derecruitment) according to the inspiratory limb of the PV curve does not have a solid physiological basis.

The positive results obtained by Amato [18] and Ranieri [41], setting the PEEP above the inflection point, may be simply explained by the higher PEEP applied in the treatment compared to the control group.

GAS-EXCHANGE TRIAL

Another easy method to perform to select the “Optimal PEEP” at bedside is the gas-exchange trial. Usually different PEEP levels from 5 to 20 cmH₂O are randomly applied in a given order (increasing or decreasing) and gas-exchange is measured. Both changes in oxygenation (PaO₂) and carbon dioxide (PaCO₂) are evaluated. An increase in oxygenation likely reflects the amount of aerated tissue present at end expiration, or on the other side, the amount of collapsed non-aerated tissue which has been maintained open at end-expiration [72]. We usually consider as a positive response of the gas exchange trial an improvement in oxygenation of at least 10-15 mmHg

(whatever inspired oxygen fraction is used). On the other side, we have to consider the behavior of PaCO₂. The value of PaCO₂ is not usually considered when a PEEP trial is performed. However, we believe that a change in PaCO₂ (at constant minute ventilation) may be more informative than changes in oxygenation. We have to remind that a change in oxygenation of 40 mmHg (*i.e.* from 60 to 100 mmHg) causes a change in oxygen content similar to the change in carbon dioxide content of 5 mmHg (*i.e.* from 40 to 45 mmHg). Our hypothesis is that when carbon dioxide decreases during the PEEP test this likely means there is prevalent alveolar recruitment, and when there is no change in carbon dioxide that means there is a balance between recruitment and overdistension, and finally even small increases in PaCO₂ likely indicate prevalent overdistension (or at least the amount of overdistension that we have to allow) compared to the amount of recruitment. Thus we believe that when a gas exchange trial is performed both oxygenation and carbon dioxide changes have to be taken into account to optimize the selection of PEEP.

RESPIRATORY MECHANICS TRIAL

Other authors have suggested to use the respiratory mechanics to select PEEP [16,73]. The best compliance of the respiratory system should indicate the level of PEEP at which the lung is maintained more open [74]. An alternative mode to select PEEP by using respiratory mechanics has been suggested by Ranieri et al. using the pressure time curve during constant flow ventilation and analyzing the shape of the curve [75]. This interesting approach, however, has not been yet validated in a clinical setting. New forms of continuous monitoring of collapse and decollapse, as with electrical impedance tomography, are still in an experimental stage [76].

Anyway, we believe that when present, improvements in respiratory compliance likely indicate more open lung tissue relative to overdistension, and no changes in respiratory compliance indicate no overdistension or an equal relationship between opening and overdistension, and finally reduction in respiratory compliance indicates a prevalent overdistension. However, this method is limited by the fact that not always respiratory compliance really parallels changes in aeration and if so, these changes are small and poorly sensitive. Moreover, the respiratory compliance cannot be representative of the lung mechanical behavior in presence of altered chest wall compliance, as found in patients with respiratory problems related to abdominal surgery [15,16] or in obese patients [77].

OXYGEN TRANSPORT

Other authors [15,78] proposed to set “optimal PEEP” considering primarily its effects on oxygen delivery. In other words they proposed to consider as the main effect of PEEP the interaction between the level of oxygenation and its effects on hemodynamics. This approach has the advantage that it is a relatively integrated approach between gas-exchange and hemodynamics. However, its limiting factor is that with this method it is possible to reach acceptable oxygen delivery (greater than 600 ml O₂/min) even with relatively low levels of PEEP that we know do not optimize alveolar opening [11]. In other words, with this method it is likely to obtain a safe oxygenation but it is very likely that the collapse and decollapse of the alveolar units continues to occur.

SELECTION OF “OPTIMAL PEEP”: AN INTEGRATED APPROACH

Recently, an integrated approach to select “optimal PEEP” have been proposed using 1) oxygenation and respiratory mechanics and 2) lung morphology by chest X ray and /or CT scan.

Oxygenation and respiratory mechanics

An interesting integrated approach of gas exchange and respiratory mechanics has been proposed by Bohm and Lachmann [79] and has recently been investigated in animal [13,80,81] and human studies [71]. It consists of a first part to open up the lung (increasing plateau pressure and PEEP levels), and a second part to keep the lung open (progressively decreasing PEEP levels).

First the ventilatory setting should be switched from volume to pressure control mode, the level of the previous inspiratory plateau pressure on volume control could serve as a guide to find the appropriate plateau pressure for pressure control ventilation. Otherwise, the plateau pressure during volume control ventilation minus 5 cmH₂O could be chosen. The levels of PEEP can initially be the same as in the first mode. With an inspiratory/expiratory ratio equal to 1:1 both PEEP levels and plateau inspiratory pressures are successively incremented in steps of 3 to 5 cmH₂O. Rarely, levels of 20/60 cmH₂O for PEEP and plateau inspiratory pressure

are necessary. During the process of opening the lungs the PaO₂ helps to guide this effort, because it is the only parameter that reliably correlates with the amount of the lung tissue that participates in gas exchange. Moreover, a more than proportional increase in the size of the tidal volume following an increase in airway pressure also indicates alveolar recruitment. It is important to maintain a sufficient intravascular volume during the maneuver (opening procedure). It may be necessary to administer fluids and give inotropic support to the right heart. This type of hemodynamic support will be superfluous at lower airway pressures.

If a further increase in airway pressure does not result in a parallel increase in PaO₂, plateau inspiratory pressures can be carefully reduced, because now reopened alveoli are present which, to keep open, no longer require such high intrapulmonary pressures. The PaO₂ should, however, remain high despite the reduction in airway pressures, just until the critical level of pressure is reached at which the least compliant parts of the lungs start to collapse. Should this occur, the inspiratory pressures should be increased again to the previously determined values for a short period. When the lung tissue is fully recruited, the pressures should then be reduced to levels which are safely above the closing pressure, usually 2-3 cmH₂O.

Oxygenation, respiratory mechanics and lung morphology

Another integrated approach has been suggested by Rouby et al. [82] by using respiratory mechanics and lung morphology. Briefly the authors performed a Chest Xray or CT scan at PEEP 5 cmH₂O. If this showed a diffuse loss of aeration (diffuse and bilateral hyperdensities “white lungs”), they performed a pressure-volume curve to determine the upper inflection point and subsequently performed a PEEP trial at 10, 15, 20 and 25 cmH₂O with a pressure limitation at 2 cmH₂O lower than the upper inflection point. If the morphological study showed bilateral hyperdensities predominating in the lower lobes, they suggested to perform a PEEP trial at 5, 8, 10 and 12 cmH₂O. The optimal PEEP level was defined as the PEEP allowing the highest PaO₂ and SatO₂ at the lowest FiO₂. If the optimal PEEP level was not reached and it did not allow to reduce FiO₂ below 0.5, other supporting mechanisms were used such as prone position, inhaled nitric oxide, almitrine trial and finally extracorporeal membrane oxygenation.

All these recommendations to select the “optimal PEEP” levels are based on the hypothesis that PEEP is not only useful to improve oxygenation, maintaining open previously collapsed alveoli, but also that PEEP is a “therapeutic” strategy to avoid collapse and decollapse of the alveolar units, preventing ventilator associated lung injury as atelectrauma and biotrauma. However, it is also possible that keeping the lung “closed”, avoiding recruitment (as in lobar pneumonia) is not dangerous and may be beneficial. Experimental studies showed that keeping part of the lung closed resulted in a decrease of lung damage compared to the control [83,84]. In our opinion we should also be ready to reconsider the use of an extracorporeal assist device [85].

OTHER VENTILATORY STRATEGIES PROPOSED TO IMPROVE OXYGENATION AND MINIMIZE VENTILATOR ASSOCIATED LUNG INJURY

Among controlled mechanical ventilation strategies, alternative strategies have been proposed. Although the physiological basis for the lung protective strategy has been well established, several questions are still open. As the tidal volume may be harmful, we might expect a decrease in lung injury using of high frequency oscillation (HFO) or high frequency ventilation (HFV). In fact it has been shown that HFV compared to the conventional mechanical ventilation resulted in lower production of inflammatory mediators [86]. Unfortunately these kinds of ventilations did not show any benefit in clinical practice [87]. However, the PEEP levels used in these studies were likely inadequate. To define the role of HFV and HFO in lung protective strategy, appropriate trials are needed [88].

Another possible improvement would be the intermittent use of higher tidal volume (sigh). When the airway pressure is intermittently increased to 45 cmH₂O, maintaining the tidal volume in the safe range, two possible advantages have been demonstrated: first, the “sigh” ventilation may prevent the development of reabsorption atelectasis, supplying fresh gas to lung regions with low ventilation/perfusion ratios; second, in the case of atelectasis the use of a “sigh” ventilation may act as recruitment maneuver [19].

Among assisted methods airway pressure release ventilation (APRV) and bilevel positive airway pressure (BiPAP) have been proposed. All of them allow an unrestricted spontaneous breathing at any moment of the respiratory cycle while the machine periodically switches between two levels of positive airway pressure. Compared to totally controlled mechanical ventilation, unrestricted spontaneous breathing superimposed on

mechanical ventilation results in an improvement in oxygenation parameters by an improvement in V/Q matching (decrease in intrapulmonary shunt and dead space) in ARDS animals [89] and in humans [90]. The diaphragmatic contraction improves the ventilation of dependent parts of the lungs (redistribution of ventilation to less aerated areas with a reduction in the pulmonary shunt). Moreover, as spontaneous breathing decreases the mean intrathoracic pressure, venous return increases and so does the cardiac output and oxygen delivery.

Therefore unrestricted spontaneous breathing superimposed on mechanical ventilation may improve ventilation of the dependent lung zones and may recruit underventilated or collapsed areas. Interestingly these effects are not observed during pressure support ventilation (PSV), a form of mechanical assistance of each inspiratory effort. The spontaneous inspiratory activity during mechanically assisted breaths during PSV is probably not sufficient to improve the ventilation of the dependent parts of the lung and to decrease the intrathoracic pressure significantly. Anyway the PSV has been shown to allow the same level of oxygenation as with controlled mechanical ventilation with much less need of sedation [91].

Another form of assisted mechanical ventilation which has been proposed to improve oxygenation in ARDS is the proportional assist ventilation [92]. Like other modes of positive pressure ventilation, proportional assist ventilation elevates airway pressure during inspiration. Unlike other modes, the inspiratory airway pressure assistance varies directly with patient effort [93]. This allows breath to breath variations in inspiratory flow and tidal volume, as with pressure support but the magnitude of the pressure assistance increases with patient effort. Moreover, the inspiratory assistance can be customized to the elastance and resistance properties of each patient's respiratory system. This mode of ventilation is most favorable for breathing comfort and for reducing unnecessary work of breathing. Studies in ARDS have shown that proportional assist ventilation can improve oxygenation compared to conventional mechanical ventilation [94].

In conclusion, assisted modes of mechanical ventilation can be useful to improve oxygenation in ARDS, perhaps comparable to or even better than conventional methods. Moreover, they need much less sedation and curarization. However, these encouraging physiological results have not been paralleled by large clinical trials indicating the effective superiority of these techniques compared to conventional mechanical ventilation.

PRONE POSITION TO IMPROVE OXYGENATION AND REDUCE VENTILATOR ASSOCIATED LUNG INJURY

Prone positioning leads to substantial improvement in arterial oxygenation in approximately 65-75% of the ARDS patients [62, 95, 96]. There is little information to predict which patients will respond positively to prone positioning. However, the improvements in some patients are quite striking, allowing a substantial reduction of the inspiratory oxygen fraction and PEEP. The mechanisms by which the prone position improves oxygenation have been investigated experimentally. It has been shown [97] that improved ventilation to previously dependent (dorsal) regions occurs in prone position. The same has been shown in humans [98]. In the supine position, pleural pressures are higher near the most dependent part of the lung due to hydrostatic pressures [5,13]. Higher pleural pressures reduce transmural pressures of the dependent bronchioles and alveoli, contributing together with other factors to the tendency for atelectasis in these zones. In the prone position, pleural pressures appeared more uniform allowing some dorsal regions to open up and participate in ventilation and gas exchange.

However, the redistribution in alveolar inflation and ventilation has to be paralleled by no change or more uniform distribution of perfusion to explain the improvement in oxygenation. Most of the data of lung perfusion in prone position arise from experimental work, direct evidence on ALI-ARDS patients is lacking. The experimental data suggest that the gravitational model does not apply in prone position. In fact, Glenny et al. showed that in the prone position the gravitational gradient is reduced with a more homogeneous distribution of blood flow, *i.e.* similar blood flow in the dependent and no dependent lung regions [99].

Thus in ALI-ARDS patients the prone position may cause a more homogeneous distribution of perfusion, relatively unaffected by the gravity. In conclusion, the available evidence suggests that the perfusion does not dramatically change when changing the position [97].

As discussed above ventilation-induced lung injury is now been widely recognized as a major problem in the management of acute respiratory failure [100]. The use of high transpulmonary pressure (*i.e.*, ventilation with high tidal volumes or high pressures) by overstretching the alveoli can cause epithelial and endothelial disruptions and induce lung edema. Besides, failure to apply adequate PEEP levels can further increase the shear forces resulting from the repeated airspace opening and closing. When ALI-ARDS patients are in the supine position, the airspace opening and closing, the largest alveolar volume excursions and the smallest end-expiratory alveolar volumes are preferentially distributed in the dorsal regions due to the more positive pleural

pressure and to the lower regional functional residual capacity. The prone position can increase the transpulmonary pressure and the regional functional residual capacity by reducing the gravitational gradient of pleural pressure. Moreover, it can limit the shear forces and the alveolar volume excursions in the dorsal regions. Similarly, the prone position causing a more homogeneous pulmonary blood flow distribution may limit the capillary stress and reduce the lung edema.

Recent animal data showed that in the prone position, either in healthy or in injured lung models, the lung edema and the severity of histologic abnormalities were less severe in prone compared to the supine position [101,102,103]. Moreover, in supine position the lung edema and the histologic abnormalities were higher in the dorsal regions while in the prone position the distribution of lung edema and histologic abnormalities were more uniform between the dorsal and the ventral regions.

It has also been shown that the prone position may reduce the incidence of pneumothorax [104].

In conclusion, the use of the prone position has a proven effect of limiting the ventilation-induced lung injury [105], besides the improvement in gas exchange, but the effects on outcome are still under investigation.

In a multicenter trial, 305 ALI-ARDS patients were randomized to be kept prone for at least 6 hours per day for a period of 10 days [62]. 152 patients were assigned to the prone group and 152 to the supine (control) group. The mortality did not differ significantly between the prone and the supine group at the end of the 10 days study period (21 vs 25 %), at time of discharge from intensive care (50 vs 48 %) or at 6 months (62 vs 59 %). In a post-hoc analysis, a significantly lower 10 days mortality rate in the prone group compared to the supine group was found in patients with the lowest PaO₂/F_iO₂ ratio (< 88 mmHg), with the highest Simplified Acute Physiologic Score (> 49) and the highest tidal volumes (> 12 ml/Kg).

These negative results could be explained by a true lack of effect of prone position on outcome or alternatively by: 1) an inadequate statistical power, 2) the short length of the prone position; an average of only 7.0 hours per day, meaning that the patients were supine for more than 70 % for each day; 3) the limitation of prone position to only 10 days.

However, considering these potential limitations, we believe that, at the present, the prone position with this protocol should not be used in all kind of ALI-ARDS patients but limited to, as suggested by the post-hoc analysis, the most severe cases of respiratory failure [106].

Two categories of ARDS patients have been poorly investigated: the trauma and the brain-injured patients, since in this case the prone position is still considered inadequate or even potentially dangerous. Recently, several studies showed the utility of prone position to improve the arterial oxygenation in trauma patients with severe respiratory failure. In these studies, different types of trauma patients were enrolled such as multiple trauma, blunt chest trauma, abdominal trauma, multiples fractures. The prone position was safe, well tolerated and caused only minor complications such as swelling and edema of the face and pressure sores. Moreover, in one study, the trauma patients with ARDS were treated for at least 20 consecutive hours per day in prone position (mean 8 ± 4 days spent in the prone position) without any significant side effects (107). Patients with intracranial pressure (ICP) > 25 mmHg despite adequate treatment and patients with unstable cervical spine fractures were excluded.

On the other hand, brain injured patients have an increased risk of extracerebral organ dysfunction, mainly pulmonary dysfunction [108]. In fact brain-injured patients are characterized by an increased risk to develop ventilator-associated pneumonia in 30 to 50 percent of cases compared to 20 percent of normal population [66,67]. Several studies indicate that pulmonary dysfunction after brain injury may significantly increase the intensive care stay, the mortality and worsen the neurological outcome [109].

The prone position has not been usually considered in brain-injured patients because of the fear of possible negative effects on brain perfusion and intracranial pressure.

Obviously, strict exclusion criteria should be considered when prone position is used: 1) presence of unstable clinical brain situation (unstable ICP, and/or ICP higher than 20-25 mmHg despite adequate treatment); 2) evidence of ischemia, as shown by a low jugular oxygen saturation level (below 55-60 mmHg).

Furthermore, in this particular group of patients we have to consider: 1) an adequate level of sedation; 2) a careful positioning of the patient in an antitrendelenburg position (the head and trunk at 20°) with a good alignment of the cervical with the thoracic spine; 3) in the more severe brain-injured patients monitoring of ICP

and jugular oxygen saturation; 4) a careful clinical monitoring of the neurologic component (in particular, the pupillary diameter in the acute phases of positioning and overall neurological status in the daily clinical assessment).

We recently investigated in a randomized controlled study the effects of a short period of prone positioning in severely brain-injured patients, sedated and paralyzed for acute respiratory failure due to ventilator-associated pneumonia [110]. During the prone position the patients markedly improved the arterial oxygenation within 4 hours and maintained the improvement in arterial oxygenation 24 hours later in the supine position. No significant increase in ICP was found during the prone position and no patients experienced an increase in ICP greater than 25 mmHg. Although these are very preliminary data, obtained in a relatively small population, during a short period of time, they suggest that the prone position in brain injured patients: 1) can be used safely; 2) improves oxygenation and the improvement is maintained for at least 24 hours while the patient is repositioned in supine position; 3) if accurately performed, with a moderate duration and carefully monitored, does not negatively affect the brain perfusion and ICP.

At present is still unknown which ALI-ARDS patients should be turned prone [111]. We suggest to turn prone the ALI-ARDS patients from the early phase of the disease and to try to maximally recruit the lung by recruitment maneuvers (RM)(*i.e.*, sighs or sustained inflations).

There are no guidelines suggesting how long the prone position should be maintained to reach the maximal beneficial effect on the respiratory function. The experiences from the literature suggest that most of the improvement occurs rapidly in only a few minutes after turning of the patient. However, an increase in arterial oxygenation can still be present even after 6 hours of prone position [62].

In some responders, the gain in arterial oxygenation is partially maintained when they return to the supine position (*i.e.*, persistent responders), while other responders suddenly lose the gain after they return to the supine position (*i.e.*, non-persistent responders) [112]. A possible explanation is that in the persistent responders the recruited lung-volume in prone is better maintained in supine comparing to the non-persistent responders.

Therefore a strategy of repeated supine-prone cycles could be useful in the persistent responders, avoiding the complication of a prolonged time of prone position. On the contrary, in the non-persistent responders we suggest to increase the length of prone position, to decrease the risk of severe hypoxemia when returning to the supine position.

RECRUITMENT MANEUVER AND PEEP DURING PRONE POSITION

The CT scan studies in supine ALI-ARDS patients showed the presence of a lung collapse not only along a vertical gradient (*i.e.*, ventral to dorsal) but also along a cephalad to caudal axis. The recruitment maneuvers (RM) are recommended as a useful tool to reopen the collapsed lung regions and to improve arterial oxygenation. However, the RM in supine position, besides to reopen the dorsal regions (*i.e.*, collapsed one) will also overdistended the already open ones. The prone position, as discussed above, by reducing the pleural pressure gradient, can increase the transpulmonary pressure in the dorsal regions. This property of the prone position causes a higher lung recruitment of the dorsal regions and higher arterial oxygenation improvement when the RM is applied in prone compared to supine position. This has been shown in experimental setting and in ALI-ARDS patients [113,19].

PEEP is one of the most important tools to increase the arterial oxygenation in severe respiratory failure. PEEP by opposing to the critical closing pressure (*i.e.*, superimposed pressure) can maintain open the lung at end-expiration. Several data suggest that PEEP in the prone position can cause a more homogeneous distribution of pulmonary blood flow compared to the supine position [114]. Due to the lower closing pressures and a more favorable pulmonary blood distribution in the prone position, lower PEEP levels are likely to be necessary to reach the same increase in the arterial oxygenation compared to the supine position [113,115].

CT scans also showed that the ventral regions remained aerated at lower PEEP levels in the prone position while the dorsal regions previously collapsed in supine position became aerated. To maintain these dorsal regions aerated in supine position, higher PEEP levels are needed and this can cause an overdistension of the ventral regions.

Indeed the prone position compared to the supine position can ameliorate the beneficial effect of a RM to increase the arterial oxygenation and requires lower PEEP levels to maintain this increase.

INHALED NITRIC OXIDE

Inhaled nitric oxide (NO) acutely improves oxygenation by dilating pulmonary vessels supplying ventilated alveolar units and improving V/Q matching [116]. It may reduce pulmonary arterial hypertension. Its short half-life in blood (around 100 milliseconds)[117] means that vascular effects are limited to the pulmonary circulation. The combination of rapid clinical improvement in some patients and lack of perceived risks had led to the widespread adoption of inhaled NO in ARDS. Three prospective controlled trials of efficacy have recently been completed. The first was a placebo controlled, blinded phase II trial of 177 patients, randomized to control or one of five treatment groups according to dosage, with therapy maintained for up to 28 days or until improvement criteria were fulfilled [118]. Transient improvements in oxygenation were detected at all doses of NO over days, but no difference in mortality was found. There was only a suggestion of an outcome difference in the number of patients successfully weaned from ventilation at day 28, when a post-hoc subgroup analysis showed that the group receiving NO 5 ppm had significantly more survivors than the control group. A smaller recent pilot study (30 patients) reflected these results [119] with no difference at 30 day mortality and a non-significant higher number of patients alive and successfully weaned from ventilation in the trial period.

Interestingly, the results of a recent prospective, double-blinded, randomized French phase III study of inhaled NO for ARDS in 208 patients also demonstrated no effect on mortality or the duration of mechanical ventilation [120].

In another recent study [121] the authors examined the ability to reduce the oxygen fraction and so to minimize the intensity of ventilation in patients on inhaled nitric oxide. No significant difference was shown in the ability of inhaled nitric oxide to reduce aggressive mechanical ventilation.

Overall all these studies suggest little benefit of long term administration of NO in ARDS. Recent published systematic historical data from Scandinavia showed no evidence of benefit in patients administered NO over a 3 year period [122].

Some authors have taken the view that NO should not be administered outside the context of controlled trials [123]. Inhaled NO is certainly efficacious in the short term and may have its place as a rescue therapy, offering a window of stability for further investigation (for example bronchoscopy), interhospital retrieval, or transfer for high resolution CT scan. In this context, it should be noted that none of the studies seemed to show any benefit in initial doses above 5-10 ppm and that, in other works, only 54% of patients showed a reproducible response, even in the acute phase [124]. A long-term supportive role is more difficult to justify especially given the risk of the toxicity and the need of monitoring of inspired nitrogen dioxide and methemoglobin levels.

Other authors proposed that other inhaled pulmonary vasodilators (for example nebulized prostacyclin) may be equally efficient as NO and easier to be administered, but they are much more expensive [125].

INHALED NITRIC OXIDE AND PRONE POSITION

NO has been shown to be beneficial in ALI-ARDS patients to increase the arterial oxygenation [126,127,128].

When NO is inhaled in the prone position it causes a greater improvement in arterial oxygenation than either treatment used alone. The improve in the arterial oxygenation can allow a faster reduction of the inspired oxygen fraction with a possible benefit in decreasing the oxygen toxicity. Furthermore the combination of prone position and inhaled NO could decrease the necessary dose of NO, so reducing the accumulation of toxic proinflammatory degradation products, such as nitrogen dioxide.

The effects of NO may be different in primary and secondary ARDS. In fact, Rialp et al. found only in primary ARDS an improvement in the arterial oxygenation with NO in the prone position [127].

However, all the studies at the present evaluated only the short term effects of inhaled NO combined in the prone position, so further studies are necessary to evaluate the real benefits of this fascinating dual therapy in the outcome of ALI-ARDS patients.

CONCLUSIONS

In conclusion, our knowledge on the pathophysiology of ARDS has dramatically increased in these last years, allowing a better tailoring of the clinical management of these patients. In early ARDS, hypoxemia is a characterizing factor of ARDS prevalently due to the presence of atelectatic and consolidated lung areas not

ventilated but relatively well perfused. Moreover, it has been emphasized that the amount of ventilatable aerated lung tissue is markedly reduced. On the other hand it has been recognized that mechanical ventilation can seriously damage the lung (ventilator associated lung injury) by several mechanisms (barotrauma/volutrauma, atelectrauma, biotrauma). The main goal is to improve oxygenation without increasing the iatrogenic effects caused by mechanical ventilation.

We have different methods now to achieve this goal, as investigated in several experimental and clinical trials. Some of these methods are related to the ventilatory setting while others are related to drug administration. Among the methods related to the ventilatory setting, those found really to be effective are: 1) the reduction of tidal volume; 2) the application of PEEP to reduce the amount of non-aerated atelectatic lung; 3) the use of the prone position, at least in more severely hypoxemic patients. On the other hand, drug administration such as the use of inhaled nitric oxide has been not found really effective.

REFERENCES

1. Ausbaugh DG, Bigelow DB, Petty TL, et al. Acute respiratory distress in adults. *Lancet* 1967; 319-323
2. Sandiford P, Province MA, Shuster DP. Distribution of regional density and vascular permeability in the adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1995;151: 737-742
3. Gattinoni L, Mascheroni D, Torresin A, et al. Morphological response to positive end-expiratory pressure in acute respiratory failure. *Intensive Care Med* 1986;12: 137-142
4. Gattinoni L, D'Andrea L, Pelosi P et al. Regional effects and mechanism of positive end expiratory pressure in early adult respiratory distress syndrome. *JAMA* 1983; 269: 2122-2127
5. Pelosi P, D'Andrea L, Vitale G et al. Vertical gradient of regional lung inflation in adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1994; 149: 8-13
6. Albert RM, Hubmayr RD. The prone position eliminates compression of the lungs by the heart. *Am J Respir Crit Care Med* 2000;16:1660-1665
7. Malbuisson LM, Brush CJ, Puybasset L et al. Role of the heart in the loss of aeration characterizing lower lobes in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2000; 161: 2005-2012
8. Froese AB, Bryan AC. Effects of anesthesia and paralysis on diaphragmatic mechanics in man. *Anesthesiology* 1974; 41: 242-254
9. Vasquez de Anda GF, Lachmann RA et al. Treatment of ventilation induced lung injury with exogenous surfactant. *Intensive Care Med* 2001; 3: 559-565
10. Puybasset L, Curiel P, Chao N et al. A computed tomography scan assessment of regional lung volume in acute lung injury. *Am J Respir Crit Care Med* 1998;198: 1644-1655
11. Gattinoni L, Pelosi P, Crotti S et al. Effects of positive end expiratory pressures on regional distribution of tidal volume and recruitment in adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1995;151: 1807-1814
12. Lachmann B. Open up the lung and keep the lung open. *Intensive Care Med* 1992; 18: 319-322
13. Pelosi P, Golden A, Mc Kibben A et al. Recruitment and derecruitment during acute respiratory failure: an experimental study. *Am J Respir Crit Care Med* 2001;164: 122-130
14. Malbouisson LM, Busch CJ, Puybasset L, et al. Role of the heart in the loss of aeration characterizing lower lobes in acute respiratory distress syndrome. *CT Scan ARDS Study Group. Am J Respir Crit Care Med* 2000; 161: 2005-12
15. Pelosi P, Cereda M, Foti G, et al. Alterations of lung and chest wall mechanics in patients with acute lung injury: effects of positive end-expiratory pressure. *Am J Respir Crit Care Med* 1995; 152: 531-7
16. Ranieri VM, Brienza N, Santostasi S, et al. Impairment of lung and chest wall mechanics in patients with acute respiratory distress syndrome: role of abdominal distension. *Am J Respir Crit Care Med* 1997;156: 1082-91
17. Gattinoni L, Pelosi P, Suter PM et al. Acute respiratory distress syndrome caused by pulmonary and extrapulmonary disease. Different syndromes ? *Am J Respir Crit Care Med* 1998;158: 3-11
18. Amato MBP, Barbas CSV, Medeiros DM et al. Effect of a protective ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998;338: 347-354
19. Pelosi P, Cadringer P, Bottino N et al. Sigh in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1999;159: 872-880
20. Foti G, Cereda M, Sparacino ME et al. Effects of periodic lung recruitment manoeuvres on gas exchange and respiratory mechanics in mechanically ventilated acute respiratory distress syndrome (ARDS) patients. *Intensive Care Med* 2000;26: 501-507
21. Lim CM, Koh Y, Park W et al. Mechanistic scheme and effect of "extended sigh" as a recruitment maneuver in patients with acute respiratory distress syndrome: A preliminary study. *Crit Care Med* 2001; 29: 1255-1260
22. Macklin MT, Macklin CC. Malignant interstitial emphysema of the lungs and mediastinum as an important complication in many respiratory diseases and other conditions: an interpretation of the clinical literature in the light of laboratory experiment. *Medicine* 1994;23: 281-352
23. Kolobow T, Moretti MP, Fumagalli R, et al. Severe impairment in lung function induced by high peak airway pressure during mechanical ventilation. *Am Rev Respir Dis* 1997;135: 312-315
24. Tsuno K, Prato P, Kolobow T. Acute lung injury from mechanical ventilation at moderately high airway pressures. *J Appl Physiol* 1990;69: 956-961
25. Dreyfuss D, Saumon G. Ventilator-induced lung injury. Lessons from experimental studies. *Am J Respir Crit Care Med* 1998;157: 294-323
26. Marini JJ, Culver BH. Systemic gas embolism complicating mechanical ventilation in the adult respiratory distress syndrome. *Ann Intern Med* 1989;110: 699-703
27. de Latorre F, Tomasa A, Klamburg J. Incidence of pneumothorax and pneumomediastinum in patients with aspiration

-
- requiring mechanical ventilatory support. *Chest* 1977;72: 141-144
28. Shnapp LM, Chin DP, Szaflarski N et al. Frequency and importance of barotrauma in 100 patients with acute lung injury. *Crit Care Med* 1995;23: 272-278
 29. Lawrence RD. Respirator induced pneumothorax and subcutaneous emphysema. Experimental overinflation of cadaver lungs. *J Forensic Sci* 1974;19:548-556
 30. Rouby JJ, Lherm T, Martin de Lassale E et al. Histologic aspects of pulmonary barotrauma in critically ill patients with acute respiratory failure. *Intensive Care Med* 1993;7: 369-371
 31. Pelosi P, Crotti S, Brazzi L et al. Computed tomography in adult respiratory distress syndrome: what has taught us. *Eur Respir J* 1996;5: 1055-1062
 32. Gattinoni L, Bombino M, Pelosi P et al. Lung structure and function in different stages of severe adult respiratory distress syndrome. *JAMA* 1994;8: 1772-1779
 33. Goldstein I, Bughalo MT, Marquette CH et al. Mechanical ventilation induced airspace enlargement during experimental pneumonia in piglets. *Am J Respir Crit Care Med* 2001;163: 958-964
 34. Gillette MA, Hess D. Ventilator induced lung injury and the evolution of lung protective strategies in acute respiratory distress syndrome. *Respiratory Care* 2001;46: 130-148
 35. Slutsky AS, Tremblay L. Multiple system organ failure: is mechanical ventilation a contributing factor ? *Am J Respir Crit Care Med* 1998;157: 1721-1725
 36. Webb HH, Tierney DF Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive end expiratory pressure. *Am Rev Respir Dis* 1974;110: 556-565
 37. Corbridge TC, Wood LDH, Crawford GP et al. Effects of large tidal volume and low PEEP in canine acid aspiration. *Am Rev Respir Dis* 1990;142: 311-315
 38. Dreyfuss D, Soler P, Basset G et al. High inflation pressure pulmonary edema: respective effects of high airway pressure, high tidal volume and positive end-expiratory pressure. *Am Rev Respir Dis* 1988;137: 1159-1164
 39. Mead J, Takishima T, Leith D. Stress distribution in lungs: a model of pulmonary elasticity. *J Appl. Physiol* 1970;28: 596-608
 40. Muscedere JG, Mullen JB, Gan K et al. Tidal ventilation at low airway pressures can augment lung injury. *Am J Respir Crit Care Med* 1994;149: 1327-1334
 41. Ranieri VM, Suter PM, Tortorella C et al. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome. *JAMA* 1999; 282: 54-61
 42. International consensus conference in intensive care medicine: ventilator-associated lung injury in ARDS. *Am J Respir Crit Care* 1999; 160: 2118-2124
 43. Tremblay L, Valenza F, Ribeiro S et al. Injurious ventilatory strategies increase cytokines and c-fos m-RNA expression in an isolated lung model. *J Clin Invest* 1997;99: 944-952
 44. Chiumello D, Pristine G, Slutsky AS Mechanical ventilation affects local and systemic cytokines in an animal model of acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1999;160: 109-116
 45. Valenza F, Sibilla S, Porro GA et al. An improved in vivo rat model for the study of mechanical ventilatory support effects on organs distal to the lung. *Crit Care Med* 2000;28: 3697-3704
 46. Haitzma JJ, Uhlig S, Goggel R. Ventilator induced lung injury leads to loss of alveolar and systemic compartmentalization of tumor necrosis factor alpha. *Intensive Care Med* 2000;10: 1515-1522
 47. Ricard JD, Dreyfuss D, Saumon G. Production of inflammatory cytokines in ventilator induced lung injury: A Reappraisal. *Am J Respir Crit Care Med* 2001;163: 1176-1180
 48. Wrigge H, Zinserling J, Stuber F et al. Effects of mechanical ventilation on release of cytokines into systemic circulation in patients with normal pulmonary function. *Anesthesiology* 2000;93: 1413-1417
 49. Ricard JD, Dreyfuss D. Cytokines during ventilator induced lung injury: A word of caution. *Anesth Analg* 2001;93: 251-252
 50. Hickling KG, Henderson SJ, Jackson R. Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. *Intensive Care Med* 1990;16: 372-377
 51. Tasker RC, Peters MJ. Combined lung injury, meningitis and cerebral edema: how permissive can hypercapnia be ? *Intensive Care Med* 1998; 24: 616-619
 52. Thorens JB, Jolliet P, Ritz M et al. Effects of rapid permissive hypercapnia on hemodynamics, gas exchange, and oxygen transport and consumption during mechanical ventilation for the acute respiratory distress syndrome. *Intensive Care Med* 1996;22: 182-191
 53. Carvalho CRR, Barbas CSV, Medeiros DM et al. Temporal hemodynamic effects of permissive hypercapnia associated with ideal PEEP in ARDS. *Am J Respir Crit Care Med* 1997;156: 1458-1466
 54. Artigas A, Bernard GR, Carlet J et al. The American-European consensus conference on ARDS. *Intensive Care Med* 1998;24: 378-398
 55. Stewart TE, Meade MO, Cook DJ et al. Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. *N Engl J Med* 1998;338: 355-361
 56. Brochard L, Roudot-Thoraval F, Roupie E et al. Tidal volume reduction for prevention of ventilator induced lung injury in acute respiratory distress syndrome. *Am J Respir Crit Care* 1998;158: 1831-1838
 57. Brower RG, Shanholtz CB, Fessler HE et al. Prospective, randomized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome patients. *Crit Care Med* 1999;27: 1492-1498
 58. The Acute Respiratory Distress Syndrome Network Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342: 1301-1308
 59. Eisner MD, Thompson T, Hudson LD et al. Efficacy of low tidal volume ventilation in patients with different clinical risk factors for acute lung injury and the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2001;164: 231-236
-

-
60. Tobin MJ. Culmination of an era in research on the acute respiratory distress syndrome. *N Engl J Med* 2000;342: 1360-1361
 61. Brower RG, Warre LB, Berthiaume Y. Treatments of ARDS. *Chest* 2001;120: 1347-1367
 62. Gattinoni L, Tognoni G, Pesenti A et al. Effect of prone positioning on the survival of patients with acute respiratory failure. *N Engl J Med* 2001;345: 568-573
 63. Richard JC, Maggiore SM, Jonson B et al. Influence of tidal volume on alveolar recruitment. Respective role of PEEP and a recruitment maneuver. *Am J Respir Crit Care Med* 2001; 163: 1609-1613
 64. Tobin MJ. Advances in mechanical ventilation. *N Engl J Med* 2001;344: 1986-1996
 65. Suter PM, Fairley HB, Isenberg M. Optimum end expiratory airway pressure in patients with acute pulmonary failure. *N Engl J Med* 1975;292: 284-289
 66. Falke KJ, Pontoppidan A, Kumar D. Ventilation with end expiratory pressure in acute lung injury. *J Clin Invest* 1972;51: 2315-2323
 67. Gattinoni L, Pesenti A, Avalli L et al. Pressure volume curve of total respiratory system in acute respiratory failure: a computed tomographic scan study. *Am Rev Respir Dis* 1987;136: 730-736
 68. Venegas JG, Harris RS, Simon BA. A comprehensive equation for the pulmonary pressure volume curve. *J Appl Physiol* 1998;84: 389-395
 69. Hickling KG. The pressure volume curve is greatly modified by recruitment. A mathematical model of ARDS lungs. *Am J Respir Crit Care Med* 1998;158: 194-202
 70. Hickling KG. Best compliance during a decremental but not incremental positive end expiratory pressure trial is related to open lung positive end expiratory pressure: a mathematical model of acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2001;163: 69-78
 71. Crotti S, Mascheroni D, Caironi P. Recruitment and derecruitment during acute respiratory failure: a clinical study. *Am J Respir Crit Care Med* 2001;164: 131-140
 72. Suter PM, Fairley HB, Isenberg MD. Effect of tidal volume and positive end-expiratory pressure on compliance during mechanical ventilation. *Chest* 1978;73: 158-62
 73. Gattinoni L, Pesenti A, Bombino M, et al. Relationship between lung computed tomographic density, gas exchange and PEEP in acute respiratory failure. *Anesthesiology* 1988;69: 824-832
 74. Sibilla S, Tredici S, Porro A, et al. Equal increases in respiratory system elastance reflect similar lung damage in experimental ventilator-induced lung injury. *Intensive Care Med* 2002;28: 196-203
 75. Ranieri VM, Zhang H, Mascia L et al. Pressure time curve predicts minimally injurious ventilatory strategy in an isolated rat lung model. *Anesthesiology* 2000;93: 1320-1328
 76. Kunst PWA, Bohm SH, Vazquez G et al. Regional pressure volume curves by electrical impedance tomography in a model of acute lung injury. *Crit Care Med* 2000;28: 178-183
 77. Pelosi P, Ravagnan I, Giurati G, et al. Positive end-expiratory pressure improves respiratory function in obese but not in normal subjects during anesthesia and paralysis. *Anesthesiology* 1999;91: 1221-31
 78. Ranieri VM, Giuliani R, Cinnella G, et al. Physiologic effects of positive end-expiratory pressure in patients with chronic obstructive pulmonary disease during acute ventilatory failure and controlled mechanical ventilation. *Am Rev Respir Dis* 1993;147: 5-13
 79. Bohm S, Lachmann B. Pressure Control Ventilation. Putting a mode into a perspective. *International Journal of Intensive Care* 1996;4: 45-55
 80. Rimensberger PC, Cox PN, Frndova H, et al. The open lung during small tidal volume ventilation: concepts of recruitment and "optimal" positive end-expiratory pressure. *Crit Care Med* 1999;27: 1946-52
 81. Rimensberger PC, Pristine G, Mullen BM, et al. Lung recruitment during small tidal volume ventilation allows minimal positive end-expiratory pressure without augmenting lung injury. *Crit Care Med* 1999;27: 1940-5
 82. Rouby JJ, Lu Q, Goldstein I. Selecting the right level of positive end-expiratory pressure in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2002;165: 1182-1186
 83. Rossi N, Kolobow T, Aprigliano M et al. Intratracheal pulmonary ventilation at low airway pressures in ventilator-induced model of acute respiratory failure improves lung function and survival. *Chest* 1998;114: 955-957
 84. Hickling KG, Timothy W, Laubscher K et al. Extreme hypoventilation reduces ventilator induced lung injury during ventilation with low positive end-expiratory pressure in saline-lavaged rabbits. *Crit Care Med* 1998;26: 1690-1697
 85. Gattinoni L, Pesenti A, Bombino M et al. Role of extracorporeal circulation in adult respiratory distress management. *New Horiz* 1993;4: 603-612
 86. Imai Y, Nokogawa S, Ito Y et al. Comparison of lung protection strategies using conventional and high frequency oscillatory ventilation. *J Appl Physiol* 2001;4: 1836-1844
 87. HIFI Study Group. High frequency oscillatory ventilation compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants. *N Engl J Med* 1989;320: 88-93
 88. Krishnan JA, Brower RG. High frequency ventilation for acute lung injury and ARDS. *Chest* 2000;118: 795-807
 89. Putensen C, Rasanen L, Lopez FA. Ventilation perfusion distributions during mechanical ventilation with superimposed spontaneous breathing in canine lung injury. *Am J Respir Crit Care Med* 1994;150: 101-108
 90. Putensen C, Mutz NJ, Putensen-Himmer G, Zinserling J. Spontaneous breathing during ventilatory support improves ventilation perfusion distributions in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1999;159: 1241-1248
 91. Cereda M, Foti G, Marcora B, et al. Pressure support ventilation in patients with acute lung injury. *Crit Care Med* 2000;28: 1269-75
 92. Brower RG, Lorraine BW, Brithiaume Y, et al. Treatment of ARDS. *Chest* 2001;120: 1347-1367
 93. Younes M. Proportional assist ventilation: results of an initial clinical trial. *Am Rev Respir Dis* 1992;145: 114-120
 94. Capra C. Proportional pressure support in acute lung injury. In: Vincent JL ed. *Year book of Intensive care Medicine*
-

-
- and Emergency Medicine, Springer-Verlag, Berlin 2001;434-435
95. Albert RK, Leasa D, Sanderson M, et al. The prone position improves arterial oxygenation and reduces shunt in oleic acid induced acute lung injury. *Am Rev Respir Dis* 1987;135: 628-633
 96. Pelosi P, Tubiolo D, Mascheroni D, et al. Effects of the prone position on respiratory mechanics and gas exchange during acute lung injury. *Am J Respir Crit Care Med* 1998;157: 1-7
 97. Lamm WJE, Graham MM, Albert RK. Mechanism by which the prone position improves oxygenation in acute lung injury. *Am J Respir Crit Care Med* 1994;150: 184-193
 98. Gattinoni L, Pelosi P, Vitale G, et al. Body position changes redistribute lung computed tomographic density in patients with acute respiratory failure. *Anesthesiology* 1991;74: 15-23
 99. Glenny RW, Lamm WJE, Albert RK, et al. Gravity is a minor determinant of pulmonary blood flow distribution. *J Appl Physiol* 1991;71: 620-629
 100. Gillette MA, Hess DR. Ventilator induced lung injury and the evolution of lung protective strategies in acute respiratory distress syndrome. *Respir Care* 2001;46:130-148
 101. Broccard A, Shapiro RS, Schmitz LL, et al. Prone position attenuates and redistributes ventilator induced lung injury in dogs. *Crit Care Med* 2000;28: 295-303
 102. Broccard A, Shapiro RS, Schmitz LL, et al. Influence of prone position on the extent and distribution of lung injury in a high tidal volume oleic acid model of acute respiratory distress syndrome. *Crit Care Med* 1997;25:16-27
 103. Safar P, Agosto-Escarraga L. Compliance in apneic anesthetized adults. *Anesthesiology* 1959;20: 283-289
 104. Yamado HDL, Orii R, Suzuki S et al. Beneficial effects of the prone position on the incidence of barotrauma in oleic acid induced lung injury under continuous positive pressure ventilation. *Acta Anaesthesiologica Scandinavica* 1997;4:701-707
 105. Albert RK. Prone position in ARDS: What do we know and What do we need to know. *Crit Care Med* 1999;11: 2574-2575
 106. Slutsky AS. The acute respiratory distress syndrome, mechanical ventilation and the prone position. *N Engl J Med* 2001; 345: 610-611
 107. Fridrich P, Krafft P, Hochleuthner H, et al. The effects of long term prone positioning in patients with trauma induced adult respiratory distress syndrome. *Anesth Analg* 1996; 83: 1206-1211
 108. Mascia L, Andrews PJ. Acute lung injury in head trauma patients. *Intensive Care Med* 1998;24: 1115-1116
 109. Gruber A, Reinprecht A. Pulmonary function and radiographic abnormalities related to neurological outcome after aneurismal subarachnoid hemorrhage. *J Neurosurg* 1998;88: 28-37
 110. Pelosi P, Colombo G, Gamberoni C, et al. Acute respiratory failure in brain injured patients. *Recent Res Devel Resp Critical care Med* 2001;1: 19-37
 111. Albert RK. The prone position in acute respiratory distress syndrome: where we are, and where do we go from here. *Crit Care Med* 1997;25:1453-1454
 112. Chatte G, Sab JM, Dubois JM, et al. Prone position in mechanically ventilated patients with severe acute respiratory failure. *Am J Respir Crit Care Med* 1997; 155: 473-478
 113. Cakar N, Van der Kloot T, Youngblood M et al. Oxygenation response to a recruitment maneuver during supine and prone positions in an oleic acid induced lung injury model. *Am J Respir Crit Care Med*; 2000;161: 1946-1956
 114. Walther SM, Domino KB, Glenny RW, Hlastala MP. Positive end-expiratory pressure redistributes perfusion to dependent lung regions in supine but not in prone lambs. *Crit Care Med*; 1999;27: 37-45
 115. Lim CM, Koh Y, Chin JY et al. Respiratory and haemodynamic effects of the prone position at two different levels of PEEP in a canine acute lung injury model. *Eur Respir J* 1999;13: 163-168
 116. Rossaint R, Falke KJ, Lopez F et al. Inhaled nitric oxide for the adult respiratory distress syndrome. *N Engl J Med* 1993; 328: 399-405
 117. Moncada S, Palmer RMJ, Higgs EA. Nitric oxide: physiology, pathophysiology, and pharmacology. *Pharmacol Rev* 1991;43: 109-142
 118. Dellinger RP, Zimmerman JL, Taylor RW, et al. Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: results of a randomized phase II trial. *Crit Care Med* 1998;26: 15-23
 119. Troncy E, Collet JP, Shapiro S, et al. Inhaled nitric oxide in acute respiratory distress syndrome: a pilot randomized controlled study. *Am J Respir Crit Care Med* 1998;157: 1483-1488
 120. Payen D, Vallet B, Group G. Results of the French prospective multicentric randomized double blind placebo controlled trial on inhaled nitric oxide in ARDS. *Intensive Care Med* 1999;25: S166
 121. Michael JR, Barton RG, Saffle JR, et al. Inhaled nitric oxide versus conventional therapy: effect of oxygenation in ARDS. *Am J Respir Crit Care Med* 1998;157: 1372-1380
 122. Luhr O, Nathorst-Westfelt U, Lundin S, et al. A retrospective analysis of nitric oxide inhalation in patients with severe acute lung injury in Sweden and Norway 1991-1994. *Acta Anesthesiol Scand* 1997;41: 1238-1246
 123. Matthay MA, Pittet JF, Jayr C. Just say NO to inhaled nitric oxide for the acute respiratory distress syndrome. *Crit Care Med* 1998;26:15-23
 124. Treggiari-Venzi M, Ricou B, Romand JA, et al. The response to repeated inhaled nitric oxide inhalation is inconsistent in patients with acute respiratory distress syndrome. *Anesthesiology* 1998;88: 634-641
 125. Putensen C, Hormann C, Kleinsasser A, et al. Cardiopulmonary effects of aerosolized prostaglandin E1 and nitric oxide inhalation in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1998;157: 1743-1747
 126. Papazian L, Bregeon F, Caillot F et al. Respective and combined effects of prone position and inhaled nitric oxide in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1998;157: 580-585
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