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Lung protective ventilation in ARDS: the open lung maneuver

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This review addresses the current state of lung protective strategies and their physiological rationale. Lung protective ventilation can reduce mortality in adult respiratory distress syndrome (ARDS) patients. We review the latest knowledge on the progression of lung injury by mechanical ventilation. Results from clinical studies on mechanical ventilation are compared with results obtained in experimental studies. Furthermore, we discuss possible future improvements to mechanical ventilation; especially the open lung maneuver. The rationale behind the open lung maneuver and steps to accomplish an open lung are described, as well as data from animal and human studies. Finally, guidelines for future strategies and/or investigations are presented.

Key words: **Adult respiratory distress syndrome - Lung - Mechanical ventilation - PEEP - Cytokines - Tidal volume - Multi organ failure.**

Adult respiratory distress syndrome (ARDS) was mentioned in an historic article by Ashbaugh *et al*. in 1967.[1] They described 12 patients with severe dyspnea, tachypnea, cyanosis, loss of lung compliance and diffuse alveolar infiltration seen on the chest X-ray. They observed and reported several clinical and pathological similarities with neonates with respiratory distress syndrome, notably surfactant dysfunction.[1] Over 40 years before the work of Asbaugh's group, von Neergaard [2] in 1929 was the first to suggest that surface tension plays a role in lung elasticity. He showed that the pressure necessary to fill the lung with liquid was less than half the pressure needed to fill the lung with air. His explanation for this remarkable difference was based on the assumption that at the interface of each alveolus there must be some retraction forces between air and fluid. This retraction force could reduce the size of the alveolus according to the law of Laplace.[2] From the law of Laplace, $P = 2\gamma/r$ (P = pressure in the bubble; γ = surface tension; r = radius of the bubble), it could be concluded that a reduction of the radius of a bubble needs an equal reduction in surface tension to keep the bubble stable, which can only be accomplished by a dynamic behavior of a surface tension lowering material, which is pulmonary surfactant.

Thus, when the endogenous surfactant system is impaired, independent of the cause, the rise in surface tension will result in atelectasis formation, enlargement of the functional right-to-left shunt, pulmonary edema, impaired gas exchange and subsequent hypoxemia.[3] These patients require mechan-

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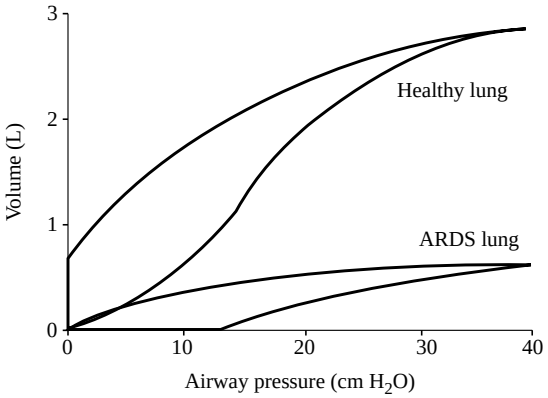

Figure 1.—Pressure volume diagram of a healthy air-filled lung and an ARDS lung. In ARDS higher pressures are required to expand the lung compared to a healthy lung due to the high surface tension at the air-liquid interface in the alveoli, which is caused by surfactant inactivity. [Adapted from von Neergaard [2]].

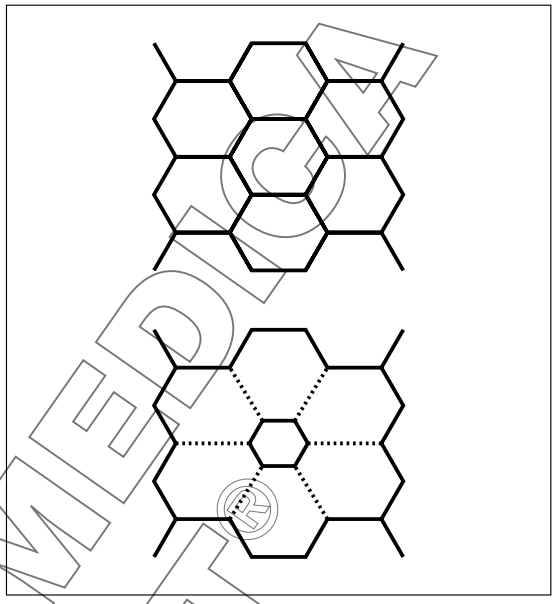

Figure 2.—Diagram showing the interdependence of alveoli. When normal alveoli are ventilated (A) forces between alveoli are equal, mechanical ventilation of the same alveolar unit after surfactant inactivation (B) results in end-expiratory collapse and subsequent shear forces on surrounding alveoli. [Adapted from Mead *et al.*[9]].

ical ventilation to decrease their work of breathing and reverse the life-threatening hypoxemia and their respiratory acidosis.[4]

What does mechanical ventilation do?

During mechanical ventilation either a fixed tidal volume (TV) is set (volume controlled ventilation) or a fixed pressure is set resulting in a TV which is dependent on the distensibility of the lung (pressure controlled ventilation). Although it is beyond the scope of this review to go into extensive details about these two types of mechanical ventilation, we will briefly discuss the advantages and disadvantages of both of them.[4-6]

The volume which enters a lung correlates with the airway pressure, and a pressure-volume (P-V) diagram will depict this for each individual lung. Figure 1 shows 2 P-V diagrams, one of a healthy lung and one of an ARDS lung.[2] To get the same volume into an ARDS lung (which is characterized by a lower distensibility) much higher airway pressures are required compared to the healthy lung; or in other words, when applying the same airway pressure more volume will enter the healthy lung than into an ARDS lung. The P-V diagram depicted in Figure 1 demonstrates that, when using pressure controlled ventilation, airway pressures need to be adapted to the individual lung thus allowing sufficient ventilation which is a prerequisite for adequate CO_2 elimination. Setting a fixed volume will indeed allow sufficient ventilation and thus adequate CO_2 elimination, but it may lead to high airway pressures in stiff (ARDS) lungs. The high airway pressures generated in ARDS lungs are further enhanced due to the inhomogeneity in distensibility of the injured lung,[7] the open and thus relatively healthy lung parts will be prone to overinflation while the injured lung areas will not be inflated. The progression of the injury to the lung will result in atelectatic lung areas and patches of still open lung tissue. When this lung is ventilated, even with small TVs, air will go preferentially to these open still compliant parts. This phenomenon has been described as a 'baby lung' and the subsequent ventilation even with small TVs will result in overdistension.[8] Depending on the amount of collapsed lung tissue even these small TVs will increase the actual TV delivered to the open lung areas several fold

(when 75% of the lung is collapsed, the open lung part will receive 4 times the volume in the open lung areas).

Pioneering work of Mead *et al.* demonstrated that, due to the pulmonary interdependence of the alveoli, the forces acting on the fragile lung tissue in non-uniformly expanded lungs are not only the applied transpulmonary pressures, but also the shear forces that are present in the interstitium between open and closed alveoli (Figure 2).[9] Transpulmonary pressures of 30 cmH_2O will result in shear forces of 140 cmH_2O.[9] Shear forces, rather than end-inspiratory overstretching, may well be the major reason for epithelial disruption and the loss of barrier function of the alveolar epithelium. In an ARDS lung there is a coexistence of collapsed alveoli, non-collapsed alveoli and alveoli that are subjected to repeated opening and closure; especially this latter category is subjected to these shear forces.[8, 9] Important evidence for this mechanism comes from the finding that ventilation even at low lung volumes can augment lung injury in lungs with an impaired surfactant system.[10, 11] Preventing repeated collapse by stabilizing lung tissue at end-expiration with positive end-expiratory pressure (PEEP) has been shown to reduce lung injury.[8, 12-14]

Role of peak pressures, TV and PEEP

Webb *et al.* in 1974 demonstrated the critical role that PEEP plays in preventing/reducing lung injury.[12] In rats ventilated with 10 cmH_2O of PEEP and a peak pressure of 45 cmH_2O no lung injury was present but using the same peak pressure and omitting PEEP severe pulmonary edema was formed within 20 min.[12] In a study by Verbrugge *et al.* the difference in pressure amplitude between these two groups also resulted in difference in TV, i.e. 18 mL/kg and 45 mL/kg in the 45/10 and 45/0 group, respectively.[13] Dreyfuss *et al.* further explored the role of TV and peak inspiratory pressures on lung injury.[15] In an animal model they applied high inspiratory pressures in combination with high volumes which resulted in increased alveolar permeability.[15] In a second group low pressures were combined with high volume (iron lung ventilation) again resulting in alveolar permeability.[15] In the third group the effect of high pressures combined with low volume was studied, by strapping the chest wall to reduce chest excursions; the permeability of this group (high-pressure low-volume group) did not differ from the control group.[15] Thus large TV ventilation increases alveolar permeability, whereas peak inspiratory pressures do not seem to influence the development of this type of lung injury. Similar observations were made in rabbits ventilated with high peak pressures in which thorax excursions were limited by a plaster cast.[16] In injured lungs the effect of higher volumes only aggravated the permeability, as demonstrated in animals in which the surfactant system was inactivated and which were subsequently ventilated with high TVs.[17, 18]

Although Webb *et al.* already demonstrated that PEEP could ameliorate lung injury,[12] the mechanism is still not clearly understood. PEEP can stent alveoli at end expiration and thus prevent repetitive collapse, reducing shear forces.[19, 20] The most important role of PEEP is to preserve surfactant function. Two basic mechanisms have been reported to explain the surfactant-preserving effect of PEEP during mechanical ventilation. The first mechanism is alteration of the surfactant film by surface area changes, already suggested in 1972.[21] Wyszogrodski *et al.* demonstrated that PEEP could prevent collapse of the alveolar surface film due to low lung volumes in no-PEEP ventilation and thus prevent alteration of the endogenous surfactant, substantiated in this model by surface tension measurement and lung compliance.[22] Later it was shown that especially large area changes result in conversion of active surfactant (large aggregates LA) into inactive surfactant (small aggregates SA), believed to be the reason for the deterioration of surfactant function.[13, 23, 24] In the model first described by Webb and Tierney, 10 cmH_2O PEEP prevents a significant conversion of large aggregates into small aggregates compared with non-ventilated controls.[13, 25] A second mechanism explaining

how PEEP preserves surfactant function, is the prevention of loss of surfactant to the proximal airways. In 1976, an *ex-vivo* model was used to show that ventilation caused movement of surfactant to the airways from the alveoli.[26] Preventing alveolar collapse and keeping the end-expiratory volume of alveoli at a higher level, prevents excessive loss of surfactant in the small airways by a squeeze-out mechanism during expiration.[13, 14, 26, 27]

Accumulation of proteins in the lung due to influx of edema results in inactivation of surfactant.[28-30] PEEP can reduce this accumulation of protein in the lung and the subsequent inactivation of surfactant. Studying the effect of two PEEP levels Hartog *et al.* subjected rats to whole lung lavage to remove the endogenous surfactant.[20] In the first group PEEP was set to prevent hypoxemia (PEEP 8 cmH_2O) and in the other group PEEP was set to prevent collapse of alveoli (PEEP 15 cmH_2O) during the lavage procedure.[20] Although there was a similar amount of surfactant left in the lungs of both groups, there was a marked increase in alveolar protein levels in the low PEEP group, resulting in inactivation of surfactant as well as a deterioration of lung mechanics.[20] Reducing protein influx, minimizing deterioration of lung mechanics and other such protective effects by ventilating with higher levels of PEEP have been reported by others.[31, 32] Different animal models have shown that ventilation with PEEP at lower TVs results in less edema than ventilation without PEEP and a higher TV for the same peak or mean airway pressure [12, 15, 33, 34] and that, more specifically, PEEP prevents alveolar flooding.[12, 13]

Cytokines, inflammatory mediators

In patients ventilated with a lung protective strategy (low TV; high PEEP), lower levels of inflammatory mediators were found;[35] these lower levels of inflammatory mediators correlated with lower levels of multiorgan failure and thus improved patient outcome.[36]

These observations that mechanical ventilation influences mediator levels and finally patient outcome are substantiated by experimental data. In a landmark article, Tremblay *et al.* demonstrated that injurious ventilation strategies could induce cytokine release.[37] Using an isolated non-perfused rat lung model they demonstrated that ventilation with high volumes (40 mL/kg bodyweight) and no-PEEP resulted in increased levels of TNF-α, IL-1β, IL-6, MIP-2, IFN-γ and IL-10; both in the presence of an inflammatory stimulus (lipopolysaccharide induced) or in a non-stimulated lung.[37] Ventilation with a lower volume (15 mL/kg bodyweight) without PEEP, resulted in only a significant effect on the above-mentioned cytokines in the pre-inflamed lung.[37] Addition of PEEP of 10 cmH_2O almost prevented this increase of cytokine release.

The observation that ventilation-induced cytokine release is dependent on the level of 'priming' of the inflammatory milieu is corroborated by other studies.[38, 39] Ricard *et al.* (in a similar set of experiments) failed to show any effect of ventilation on cytokine releases without a prestimulus.[38] Similarly Verbrugge *et al.* could not demonstrate any release of TNF-α during different ventilation strategies *in vivo* in healthy lungs.[39]

In contrast, ventilation of an "inflamed" lung has been shown to result in release of cytokines.[37, 38, 40] One of the proposed mechanisms for increased mediator levels found in injuriously ventilated lungs or in the serum of these animals is the loss of compartmentalization.[25, 41, 42] The concept of compartmentalization states that the inflammatory response remains compartmentalized in the area of the body where it is produced, i.e. in the alveolar space or in the systemic circulation.[25, 41, 42] Recently, our group demonstrated that compartmentalization of TNF-α (a proinflammatory cytokine) is lost after ventilator-induced lung injury.[25] This loss of compartmentalization is dependent on the amount of active surfactant present at the alveolar-capillary membrane.[41] Preserving the endogenous surfactant system with PEEP will (further) reduce this loss of compartmentalization.[41]

Imai *et al.* in a rabbit acid-aspiration lung

injury model demonstrated that ventilation without PEEP and high TV resulted in increased levels of end-organ epithelial cell apoptosis (injurious ventilation 10.9%; non-injurious 1.86%).[43] Kidneys are amongst the first organs to fail during multi-organ failure,[44] in this study especially renal tubular epithelial cells showed increased levels of apoptosis linking injurious ventilation with possible organ failure as observed in many patients with ARDS.[43] Plasma obtained from the rabbits that underwent the injurious ventilation strategy induced higher levels of apoptosis in cultured renal cells *in vitro*, suggesting that circulating soluble factors associated with the injurious mechanical ventilation might be involved in this process.[43] Fas:Ig, a fusion protein that blocks soluble Fas ligand (a pro-apoptotic molecule), attenuated this induction of apoptosis *in vitro*. In plasma samples from patients included in a previous randomized controlled trial [35, 36] lower levels of soluble Fas ligand were found in the group ventilated with a lung protective ventilation compared to the conventionally ventilated group.[43] These data link together distant organ changes/failure and mechanical ventilation.

Injurious ventilation strategies besides inducing an inflammatory response in the lung, also downregulate the peripheral immune response.[45] Vreugdenhil *et al.* observed a decrease in MIP-2 and IL-10 production, splenocyte proliferation, splenic natural killer cell activity and interferon-gamma production during injurious ventilation.[45] Again demonstrating that besides a local effect on the lung itself, injurious ventilation also affects other cells and organs.[45]

Mechanical ventilation clinical trials

In 1990 Hickling *et al.* demonstrated that mechanical ventilation could influence mortality in ARDS patients.[46] Lowering TV in a retrospective study of 50 ARDS patients decreased mortality.[46] The outcome of this study sparked renewed interest in lowering TV in ARDS patients. Three subsequent controlled trials using low TV strategies were simultaneously started but all failed to improve patient outcome.[47-49] These studies used a TV of approximately 7 mL/kg in their low TV arms and a TV of 10 mL/kg in their control arms.[47-49] In contrast, using a TV of 6 mL/kg in their lung protective arm and a TV of 12 mL/kg in their control arm (TV calculated by using predicted bodyweight) the ARDS network was able to reduce mortality.[50] The explanation given by the ARDS network trial for the beneficial effect on mortality was the greater difference in TV between the two arms of the study, the power of the study (ARDS network studied 861 patients while the other 3 studied a maximum of 120 patients), and the aggressive treatment/prevention of acidosis.[50] The only other randomized controlled trial to show a reduction of mortality in ARDS patients had been published 2 years earlier. Amato *et al.* reported that mortality in 53 patients was significantly reduced by applying a protective ventilation strategy.[51] In their study TV was also reduced to below 6 mL/kg in the low TV group compared to 12 mL/kg TV in the control arm. In contrast to the three negative studies [47-49] the PEEP level in the low TV group of Amato *et al.*[51] was significantly higher i.e. almost 17 cmH_2O compared with 8-10 cmH_2O PEEP in the studies by Brochard *et al.*,[47] Brower *et al.*[48] and Stewart *et al.*[49] (Figure 3). Experimental data have shown that ventilation with low TVs by itself does not prevent lung injury and may even worsen lung injury when repeated collapse of lung tissue is not prevented.[10] In the ARDS network trial the low TV group had a slightly higher set PEEP of 9 cmH_2O compared to a set PEEP of 8 cmH_2O in the control group.[50] However, the increased respiratory rate (to help prevent acidosis) used in the low TV group may have resulted in intrinsic PEEP which contributed to a higher total PEEP (16 cmH_2O) in this group [52, 53] compared to 12 cmH_2O in the traditional TV group. This higher total PEEP could help explain the decrease in mortality observed in this group (Figure 3). Furthermore, in the ARDS network study only 12% of the screened patients were randomized while the mortality in the excluded group was higher than those included in the trial.[54, 55]

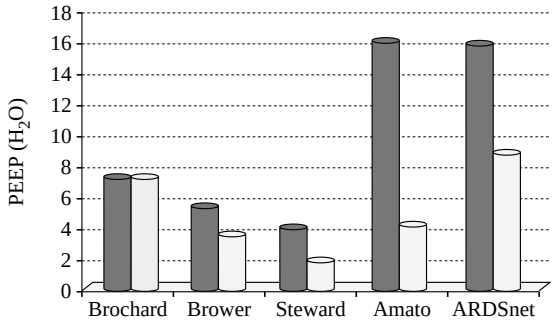

Figure 3.—Total PEEP levels applied in studies on protective mechanical ventilation. Studies used are by Brochard *et al*.,[47] Brower *et al*.,[48] Stewart *et al*.,[49] Amato *et al*.[51] and the ARDSnet [50] with intrinsic PEEP modification from De Durante *et al*.[52, 53] Black bars represent the PEEP levels in the lung protective strategies and the white bars the PEEP levels of the control arms of the corresponding studies.

In 2004 the ARDS Network published their follow-up study, investigating if increased PEEP levels combined with low TV ventilation affects outcome compared to the low TV ventilation used in their previous study.[56] The data and safety monitoring board stopped the trial at the second *interim* analysis, after 549 patients had been enrolled, on the basis of the specified futility stopping rule. Although in this study no benefit in outcome was observed between the patient groups, the mortality rate in both study arms was reduced (24.9%; lower PEEP and 27.5%; higher PEEP).[56] Again confirming that adjusting the ventilatory settings decreases mortality in ARDS/ALI patients. Unfortunately patients randomized to the higher PEEP group also had at baseline more characteristics that predict a higher mortality, adjustment for these differences in baseline covariates did not alter the final outcome but did favor the higher PEEP group.[56]

PEEP levels currently employed in intensive care units around the world are below 6 cmH_2O in 78% of the patients receiving mechanical ventilation.[57] Even more disturbing is that in the same study only three patients of the 1 638 ventilated patients studied had a PEEP level above 15 cmH_2O.[57] Whereas it is known that high PEEP levels above 15 cmH_2O are necessary to prevent repetitive collapse of alveoli and thus reduce shear forces.[19] Furthermore, only studies using PEEP levels above 15 cmH_2O in their protective arm have demonstrated a reduction in mortality.[35, 50-52]

Why do patients with ARDS die?

Although ARDS is characterized by $PaO2/FiO_2$ ratio in the American-European Consensus conference on ARDS,[58] patients do not die from hypoxemia but rather die from multi-organ failure.[55, 59] Ranieri *et al.* in 2000 linked increased levels of serum inflammatory mediators to organ failure in patients suffering from ARDS.[36] These increased serum levels of inflammatory mediators were observed in patients ventilated with conventional ventilation; in contrast a lung protective ventilation strategy (high PEEP, low TV) minimized the inflammatory response and subsequently had a lower incidence of organ failure.[35, 36] As discussed earlier, ventilation can induce mediator release especially in susceptible lungs (e.g. inflamed). Increased levels of cytokines in the serum were also observed in the ARDS network trial, in which higher levels of IL-6 were observed after 3 days of ventilation in the control arm compared to the reduced TV.[50] Similarly, the number of days without non-pulmonary organ or system failure (circulatory, coagulation and renal failure) was significantly higher in the group treated with lower TVs.[50] Increased levels of inflammatory mediators correlate with the development of ARDS [60] and high broncho-alveolar lavage levels of these mediators in ARDS lungs have been described extensively.[61-63] Furthermore, persistent high levels of inflammatory mediators in the lung over time correlate with poor outcome.[64] Similarly, plasma levels of inflammatory mediators correlate with severity of ARDS and subsequently outcome.[64, 65] Headley *et al.* investigated the role of inflammatory plasma cytokines during infections and systemic inflammation, and the subsequent development and progression of ARDS.[65] The final outcome of ARDS patients correlated with the magnitude and duration of the host inflammatory response in the serum and was independent of the precipitating cause of

ARDS or the occurrence of infections.[65] Similar observation were made in multiple trauma patients in which high concentrations of cytokines correlated with the development of ARDS and finally multi-organ failure.[66] Our group has demonstrated that injurious mechanical ventilation can result in loss of a compartmentalized inflammation response and thus increasing serum levels of inflammatory mediators;[25] similar observations were made by Chiumello *et al.*[40] Especially in the early stage of an inflammation the response will be compartmentalized, as observed in community-acquired pneumonia.[67]

In healthy patients no effects on plasma levels of mediators were observed during 1 h of mechanical ventilation; even ventilation with high TVs on ZEEP did not result in higher cytokine levels compared with lung-protective ventilatory strategies.[68] Previous lung damage seems to be mandatory to cause an increase in plasma cytokines after 1 h of high TV ventilation.[68]

Thus, in ARDS there is an inflamed lung with increased levels of proinflammatory mediators, and ventilation itself can increase the amount of inflammatory mediators produced by the lung. When the barrier function of the alveolar-capillary membrane is lost this will result in leakage of mediators to the circulation (decompartmentalization). The subsequent increased levels of these mediators in the circulation correlate with multi-organ failure and finally mortality. Use of lung protective ventilation in both experimental and clinical studies has demonstrated a reduction in the cyclic collapse of the lung which in turn reduces organ failure and mortality.

Lung protective ventilation

In an ARDS lung or a lung that is susceptible to develop ARDS a higher level of inflammation is present. When these lungs are mechanically ventilated, ventilation that will increase the inflammation response should be minimized and the barrier function of the lung should be preserved. Using a lung protective ventilation, the outcome of these patients can be improved. So what guidelines or rules should we use in lung protective ventilation? Especially ventilation with large TVs combined with end-expiratory alveolar collapse and the subsequent appearance of shear forces should be minimized. However, additional guidelines could help to reduce mortality even further. In 1982 and 1992 Lachmann suggested such a ventilation strategy.[6, 69] In the 1992 editorial entitled: "Open up the lung and keep the lung open" he explained his lung protective guidelines.[69]

There are 3 steps to open the lung as described by Lachmann:[69] 1) a critical opening pressure must be overcome during inspiration; 2) this opening pressure must be maintained for a sufficiently long period of time; 3) during expiration, no critical time that would allow closure of lung units should pass, by using auto or intrinsic PEEP or applying sufficiently high PEEP levels which prevent alveolar collapse.

The implied rationale, however, is a matter of debate: Why should we "open the lung"? What is an "open lung"? In addition, questions concerning the methodology were asked: How can we "open the lung" and how can we keep the lung open with the least possible side effects? And, finally, how can we characterize an open lung?

What is an open lung and why should it be opened?

When a lung is "open" it is characterized by an optimal gas exchange [69] and a low rate of intrapulmonary shunting (ideally less than 10%) corresponding with a PaO_2 of more than 450 mmHg on pure oxygen.[70] At the same time, airway pressures are at the minimum that ensure the required gas exchange; hemodynamic side-effects are thus minimized.[69] All alveoli are almost equally expanded, minimizing shear forces between closed and open alveoli reducing any further damage or progression of lung injury. An open lung corresponds with the "normal" state of a healthy lung. All alveoli are expanded, and although they change size during respiration no alveoli collapse. Ashbaugh *et*

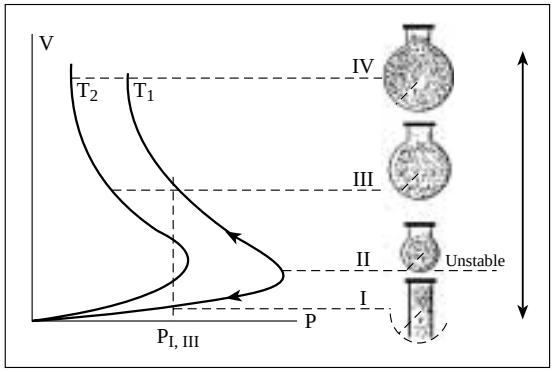

Figure 4.—Physiological behavior of the alveolus. The pressure-volume (P-V) relation is shown on the X-Y axes. The right side shows the status of the broncho-alveolar unit: its radius (r) reflects the P-V relation (I-IV). Surface tension in pathological (T1) and normal conditions (T2) is shown. The arrows indicate the direction from closed (bottom) to open (top) states and *vice versa*.

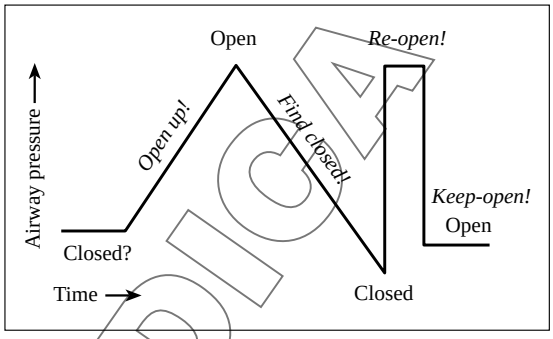

Figure 5.—Schematic representation of the opening procedure for collapsed lungs. Note: the imperatives (!) mark the treatment goal of each specific intervention. The bold words mark the achieved state of the lung. At the beginning the precise amount of collapsed lung tissue is not known.

al. already described the consequences of closed lung units; hypoxemia, intrapulmonary shunt and atelectasis, with a high risk of infection, multi-organ failure and finally death.[1] Thus an open lung has no (or minimal numbers of) collapsed alveoli. In ARDS/ALI atelectasis is a hallmark of the disease,[58] so the first step in an open lung is to open up the atelectatic areas.

Recruiting the lung

To recruit the collapsed alveoli to improve gas exchange a high opening pressure is needed. The rationale behind the high opening pressure to recruit the lung and the need for lower pressures to keep the alveoli open can be deduced from the P-V curve of an individual alveolus (Figure 4). The behavior of an alveolus is quantal in nature; it is either open or closed.[71] A critical opening pressure has to be reached before previously collapsed alveoli can be opened. Once open, alveoli remain open until the pressure drops below a critical level and immediate collapse occurs. Re-opening again requires the high recruiting pressure. Any state between open and closed is unstable and impossible to maintain. After opening of the alveoli, they should be kept open by using a ventilator setting which will keep the pressure above the critical closing pressure of the alveolus i.e. with a sufficient high PEEP level. Because the alveoli are open during the whole ventilation period no collapse of alveoli occurs, reducing shear forces to a minimal level.

Open lung maneuver

The open lung maneuver describes the steps and methods used to safely open the lung and how to keep it open. Figure 5 shows the predetermined sequence of therapeutic phases, each with its specific treatment objective.[69, 72] As shown in Figure 5, the goal of the initial increase in inspiratory pressure is to recruit collapsed alveoli and to determine the critical opening pressure. Then, the minimum pressures that prevent the lung from collapse are determined. Finally, after an active re-opening maneuver sufficient pressure is applied to keep the lung open.

After opening the lung and finding the lowest pressure to keep it open, the resulting pressure amplitude is minimized and at the same time pulmonary gas exchange is maximized. A reduction of the total level of support is generally possible after a successful alveolar recruitment.[73]

Should a renewed collapse of alveoli occur, often caused by intrapulmonary suction or disconnection, a fall in PaO_2 indicates that a

re-opening maneuver has to be performed in the same way as previously described.

Monitoring an open lung: direct methods

The most direct way to know whether a lung is completely open is to visualize the lung itself. This can be accomplished by means of radiology. The classic method of a frontal chest X-ray gives a fast and easy indication of the state of the lung. However, the technique used for obtaining a frontal chest film severely restricts this method. If the chest X-ray is taken during inspiration for normal diagnostic purpose, lung areas open on the film can be collapsed during expiration (not enough PEEP) in the same lung. Therefore to differentiate if a lung is open, it is mandatory that all chest X-rays should be made during expiration to see the amount of atelectasis still present in a lung. Furthermore, patients with a severe lung injury require high levels of PEEP generated in part by extrinsic-PEEP, a longer period of expiration (expiration hold) during the shooting of the film could lead to progressive collapse of alveoli due to loss of this extrinsic part of the total amount of PEEP. Finally there are limitations to what can be seen on a chest X-ray, especially atelectasis in the dependent parts of the lungs can be difficult to see.

A much better though more cumbersome technique is the use of computer tomography (CT) or magnetic resonance imaging (MRI). These techniques allow optimal visualization of individual lung areas and can even produce almost movie-like images of the lung in motion during ventilation.[74] However both these techniques are not readily available on the IC ward and demand transportation of these patients to other wards resulting in a less convenient and expensive technique to find out whether a lung is open.

A relatively simple technique which can be used at the bedside of patients to visualize the aeration of lung is electrical impedance tomography.[75] In this technique changes in impedance due to lung volume changes in a 2-D image plane are registered and plotted against time. Using this technique the lower inflection point and upper deflection point can be determined which correspond with traditional P-V curve points which help determine the total amount of lung recruited (i.e. open).[75] Although this latter technique shows great promise as a bedside tool to characterize an open lung, it is now only used experimentally and needs further development and validation to obtain its rightful place as a bedside tool. A similar technique is the use of optoelectric plethysmography, in this technique thorax volume changes are recorded by reflective markers positioned on the body and recorded through cameras on an automatic motion analyzer.[76] This technique has shown to accurately register volume changes during respiration. However,[45] markers are placed on the body requiring accurate positioning and the line of site of these markers and the registration cameras should not be interrupted (by sheets or other registration devices, etc.).[76]

Besides the direct methods, a number of indirect methods exist which can help determine the state of the openness of the lung.

Indirect methods

Arterial oxygen tension is a traditional tool used to obtain indirect information on the lung function. When using 100% oxygen an arterial oxygen tension above 450 mmHg characterizes an open lung. The registration of PaO_2 by continuous online intra-arterial measurements facilitates this process. Because direct intra-arterial measurements quickly respond (seconds) to changes in oxygenation, this allows rapid adjustment of ventilation. Furthermore, when recruitable lung areas are still available a further recruitment procedure will result in an additional rise of PaO_2. When the maximal recruitment has been reached a further increase of inspiratory pressures will not lead to a further rise in arterial oxygenation, indicating that the lung is open. When the inspiratory pressures are increased even further this will lead to a decrease in PaO_2 because of V/Q mismatching. With this very sensitive technique even

small pockets of atelectasis can be actively recruited.

Finally, when searching for the minimal pressure needed to maintain an open lung, a decrease in pressures below the critical closing level will result in an immediate decrease in arterial oxygenation.

In principal one can use any FiO_2 that one deems safe, but especially in critically ill patients (ARDS) this could lead to a (temporary) period of severe hypoxia, when searching for the closing pressure. Furthermore at a high FiO_2 level it is easier to recognize small atelectasis which could be missed at lower FiO_2 levels due to the inherent margin of error of every machine. Therefore we would advocate the use of an FiO_2 of 1 which can afterwards be reduced to safe margins. This technique is easier with an intra-arterial oxygen sensor, transcutaneous saturation sensors messengers can serve as a non-optimal online alternative.

If offline arterial blood gases can also be used, this will require frequent sampling during the establishment of an 'open lung'. It is also mandatory that arterial blood gas sample handling should be using strictly adhered to preventing any air bubbles in the sample. Because high oxygen values will rapidly equilibrate to the partial oxygen tension of the room, this leads to misinterpretation of results, and thus unnecessary adjustments of the ventilation.

Besides arterial oxygenation the determination of the functional residual capacity (FRC) can help establish how "open" a lung is. The interpretation of this measurement should not be done without a corresponding arterial blood gas measurement. However, an increase of FRC will not always be due to an increase of recruitable lung area (e.g. atelectasis), it can also be due to overinflation of a still reduced FRC. The corresponding PaO_2 will tell immediately if it was recruitment or overinflation. This overinflation of FRC has also been referred to as the 'baby lung'.[8] Overinflation of the baby lung can lead to ventilator-associated lung injury and subsequent worsening of the lung injury.[8]

Another simple method, which is very effective in opening larger atelectatic areas, is the use of the physician's best friend 'the stethoscope'. When listening to the lung the presence of crackles and crepitant rales indicate that during ventilation alveoli are still collapsing and actively reopened in the subsequent inspiratory phase and shifting of alveolar edema, which are clear indications that the lung is not completely open during the whole ventilation cycle.[77] In an 'open lung' these sounds will not be present. These crackles can best be heard in the dependent lung areas; it can however be difficult to distinguish the crackles in a mechanically ventilated patient from other sounds in the noisy environment of an ICU. Moreover, this technique will not allow easy detection of small pockets of atelectasis, and solely relying on this technique will lead to an incomplete recruitment procedure of a ventilated lung. However, it will always inform you that the applied PEEP level is too low. Investigations are taking place to develop a computerized respiratory sound analysis system which would offer a standardized descriptive and evaluation of lung sounds, in healthy as well as unhealthy ones.[78]

P-V curves

As stated before, the behavior of an individual alveolus is quantal in nature, either open or closed. However the P-V curve of a lung is the accumulation of millions of these alveoli. Looking at a P-V curve a distinct inflation and deflation curve can be seen. When the lung collapses the remaining volume will be almost zero, increasing the pressure will lead to a rise in volume. When a P-V curve is obtained during ventilation (most common) a period of active recruitment of collapsed alveoli will lead to an increase in volume as can be observed by an increased slope of the inflation limb. Finally the slope of the inflation limb will flatten which can be interpreted as maximal recruitment, and subsequent deflation will lead to the characteristic deflation curve. However, as shown in Figure 6, it is possible that not all recruitable lung tissue has been recruited at the used pressure, and a further increment of the pressure results

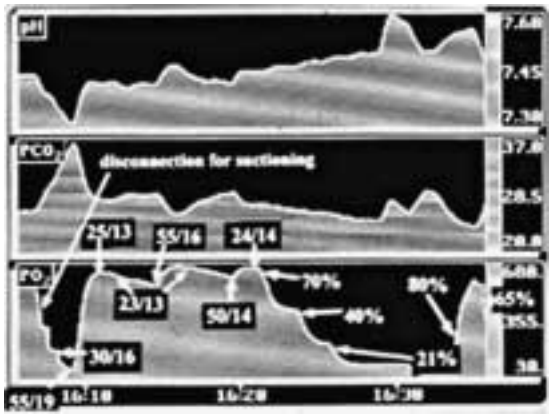

Figure 6.—Online intra-arterial registration of PaO_2, $PaCO_2$, and pH at an FiO_2 of 1 in a lung with severe lung injury. The lung is 'disconnected for suctioning', the used pressure of 30/16 (Pip/PEEP) is not enough to prevent alveolar collapse, within 2 min PaO2 drops from 680 mmHg to 50 mmHg. An opening pressure of 55/19 is needed to reopen the collapsed alveoli. A subsequent reduction of pressure to 23/13 is not enough to stabilize the reopened airways. Another increase of the Pip to 55 cmH_2O is needed to reopen the collapsing alveoli. A pressure of 24/14 can then be used to stabilize the alveoli. After this the FiO2 is reduced stepwise from 1 to 0.7, 0.4 and finally 0.21 (air), without changing pressures. Oxygenation is then 100 mmHg, an increase in FiO_2 leads to a rapid rise of arterial oxygenation values. Of note, the procedure of active recruitment and reduction of FiO_2 to room air values took less than 15 min. During this procedure the formation of small atelectasis observed during reduction of pressures to 23/13 resulted in an immediate drop of PaO_2 which led to an active readjustment of the used ventilation parameters.

in an additional increase of arterial oxygenation and a recruitment of still collapsed alveoli. Translating this to the P-V curve means that increasing the pressure on this lung even further would lead to an additional increase in volume (*e.g.* recruitment) and a stepwise inflation limb of the P-V curve. If this second recruitment procedure with higher pressures had not been performed, the original P-V curve would be considered as the representative curve of this lung, without obtaining the P-V curve corresponding with an 'open lung'. Thus, although P-V curves can give additional information on the state of the lung, they cannot be used as an indication about the openness of the lung.

Figure 7 shows the pressure volume (P-V) relationship of the lung, representing the cumulative behavior of all alveoli. The inflation limb of the P/V curve shows the changes in lung volume during incremental airway

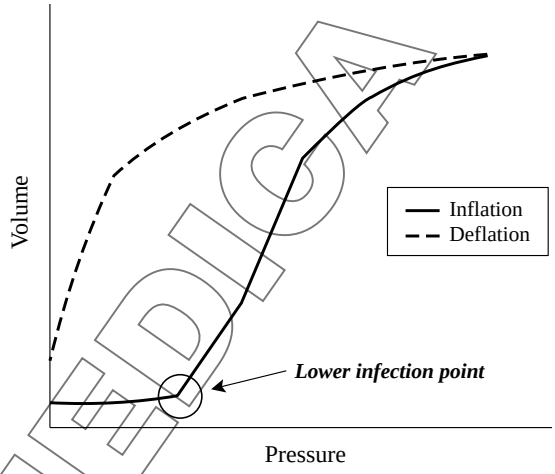

Figure 7.—Pressure-volume relationship of the lung showing the inflation (solid line) and the deflation limb (dashed line). Note the clear difference in lung volume between both limbs at identical pressures.

pressures and usually contains a so-called lower inflection point above which lung volume suddenly increases in a linear fashion. As lung volume approaches total lung capacity (TLC) the inflation limb flattens off. The deflation limb represents the changes in lung volume during decremental airway pressures starting at TLC. As explained by the law of Laplace, which states that the pressure (P) necessary to keep a spherical structure opened is two times the surface tension (γ) divided by the radius (r), lung volume is initially maintained (increased radius) as pressures are lowered but eventually decreases due to progressive alveolar collapse.

Mathematical models and animal experiments have shown that adequate recruitment of collapsed alveoli, followed by optimal stabilization with adequate levels of PEEP, will place ventilation on the more compliant deflation limb of the P-V curve.[79, 80]

Experimental data on open lung ventilation

The cornerstones of lung protective ventilation strategies are prevention of both alveolar overdistension and collapse (atelectasis). The strategies are also referred to as "optimal volume strategy" or "open lung ven-

tilation".[68] Animal studies have shown that reducing alveolar overdistension by limiting TVs during mechanical ventilation will attenuate ventilator-induced lung injury (VILI) assessed by pulmonary edema and inflammation.[15, 37]

In reducing atelectotrauma, two basic principles should be considered. First, already collapsed alveoli need to be recruited by applying sufficient airways pressures. Secondly, after recruitment sufficient end-expiratory pressure should be applied in order to prevent subsequent collapse during expiration. Failing to recruit the lung prior to increasing PEEP will not prevent VILI.[80] On the other hand, recruiting the lung but applying insufficient PEEP in order to prevent subsequent collapse will augment rather than reduce lung injury.[81] Application of an optimal lung strategy was first widely applied during high-frequency ventilation (HFV). During this mode of ventilation TVs are equal to or less than the anatomic dead space, thus minimizing volutrauma using a specific (dedicated) ventilator. However, animal studies have shown that HFV only attenuates VILI when combined with optimization of lung volume (recruitment).[82, 83] Data on lung protective ventilation using positive pressure ventilation (PPV) are scarce.

We therefore recently evaluated open lung PPV in several models of lung injury. During open lung PPV collapsed alveoli were actively recruited by applying high PIP for a short period of time and thereafter stabilized using the lowest possible airway pressures. Applying this ventilation strategy optimized gas exchange and attenuated VILI compared to conventional PPV.[84-86] Furthermore, these beneficial effects were comparable to open lung HFV, indicating that the ventilation strategy is more important in reducing VILI than the ventilation mode (PPV or HFV). Especially lung inflammation was prevented using open lung ventilation.[85] In a separate experiment we also investigated the effect on bacterial growth and translocation in group B streptococcus pneumonia model.[87] Optimizing ventilation with this strategy also reduced bacterial colonization of the lung, and reduced bacterial translocation improving survival of animals with respiratory distress.[87] A follow-up study showed that also the inflammatory response was attenuated in this model.[88] As previously explained lung inflammation is seen as a major risk factor for the outcome in ARDS.[35, 43]

Human data on the open lung

There is only limited data available on open lung ventilation in patients. Amato *et al.* in 1998 reported on a trial using a setting similar to the open lung maneuver.[51] Patients (53 with early ARDS) were randomly assigned to conventional or protective mechanical ventilation. Protective ventilation involved a recruitment maneuver, end-expiratory pressures above the lower inflection point on the static P-V curve, a TV of less than 6 mL/kg, driving pressures of less than 20 cmH_2O above the PEEP value, permissive hypercapnia, and preferential use of pressure-limited ventilatory modes.[51] As compared with conventional ventilation, the protective strategy was associated with improved survival at 28 days (38% *vs* 71%), a higher rate of weaning from mechanical ventilation (66% *vs* 29%), and a lower rate of barotrauma (7% *vs* 42%), in patients with ARDS.[51] Although several guidelines of the open lung maneuver were followed, lungs of the patients were not totally recruited (as indicated by the $PaO2/FiO_2$ ratio) this is in part due to the uniformly applied recruitment pressure of 35 to 40 cmH_2O of continuous positive airway pressures for 40 s, which is insufficient for more severe atelectatic areas to open.

In a recent retrospective analysis of patients with ARDS due to pulmonary contusion Schreiter *et al.* showed that mechanical ventilation according to the open lung maneuver dramatically improved oxygenation and lung aeration.[89] This results in low TVs of 3.5 (3; 3.9) mL/kg bodyweight.[90] Schreiter *et al.* carefully monitored lung recruitment by both arterial oxygenation and thoracic helical computed tomography scans before and after ventilation with the open lung maneuver.[89] The recruitment

reduced atelectatic areas from 604 mL to 106 mL and increased the normally aerated volume from 1 742 mL to 2 971 mL.[89] Furthermore, arterial oxygenation levels were stable after the recruitment procedure thus minimizing the cyclic opening and collapse which augments cytokine release.[10, 37, 91] The severity of the injury in the patients studied by Schreiter *et al.* is illustrated by the Acute Physiology and Chronic Health Evaluation II (APACHE II) of 23 (range, 11-26) points. The predicted mortality of the APACHE II score was 49.7%, and the adjusted APACHE II had a predicted mortality of 22.4%. These rates correspond with the respective mortality rate observed in ARDS patients (42%) [92] and in ARDS due to pulmonary contusion (20%).[93] However, all patients in the study by Schreiter *et al.* survived and were alive up to of 14-60 months after treatment for ALI/ARDS.[89]

One of the possible side effects of open lung ventilation could be cardiac impairment by high mean airway pressures. Since the open lung maneuver is a method of ventilation intended to maintain end-expiratory lung volume by increased airway pressure, this could increase right ventricular afterload. Reis Miranda *et al.* recently studied the effect of the open lung maneuver on right ventricular afterload in patients after cardiac surgery.[94] Patients were randomly assigned to open lung concept (OLC) or volume-controlled ventilation with a PEEP of 5 cmH_2O. Cardiac index, right ventricular preload, contractility and afterload were measured with a pulmonary artery thermodilution catheter during the 3-h observation period. To achieve an open lung, recruitment attempts were performed with a peak pressure of 45.5 cmH_2O.[94] To keep the lung open, PEEP of 17 cmH_2O was required. Compared with baseline, pulmonary vascular resistance and right ventricular ejection fraction did not change significantly during the observation period in either group. No evidence was found that ventilation according to the OLC affects right ventricular afterload in normovolemic patients.

These studies demonstrate that applying open lung ventilation is feasible in patients.

Future direction of the open lung maneuver

Improving mechanical ventilation has been shown to reduce mortality in patients. Although current guidelines focus on reducing TVs and minimizing mean airway pressures, other steps could be taken to improve mechanical ventilation even further. The open lung maneuver guides physicians through these steps. Using recruitment maneuvers to optimize mechanical ventilation and sufficient high PEEP levels to maintain (re)aerated lung tissue a further reduction in mortality of ARDS patients could be achieved. Current data (both animal and human) warrant a multi-center prospective randomized trial. Meanwhile, physicians should implement further optimization of their ventilation strategies, with the guidelines of the open lung maneuver.

Riassunto

Ventilazione polmonare protettiva nella sindrome da distress respiratorio dell'adulto (ARDS): l'open lung maneuver

Questa revisione si occupa dello stato attuale delle strategie protettive nei confronti del polmone e dei loro principi razionali fisiologici. La ventilazione polmonare protettiva può ridurre la mortalità nei pazienti con sindrome da distress respiratorio dell'adulto (acute respiratory distress syndrome, ARDS). In questa sede, esamineremo i più recenti sviluppi sulla progressione del danno polmonare da ventilazione meccanica. Confronteremo i risultati ottenuti dagli studi clinici sulla ventilazione meccanica con quelli ottenuti negli studi sperimentali. Inoltre, discuteremo il possibile miglioramento futuro della ventilazione meccanica, in special modo dell'open lung maneuver. Descriveremo la condotta razionale dell'open lung maneuver e i vari passi per raggiungere un open lung, così come i dati ricavati da studi eseguiti su animali e sull'uomo. Infine, presenteremo le linee guida per le strategie e/o studi futuri.

Parole chiave: Sindrome da distress respiratorio dell'adulto - Polmoni - Ventilazione meccanica - PEEP - Citochine - Volumi respiratori - Insufficienza multi organo.

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