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Treatment and Prevention of Acute Respiratory Failure: Physiological Basis

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Acute respiratory failure is caused by many factors and remains one of the most common reasons for admission to the intensive care unit (ICU). In all cases of acute respiratory failure, there is a shortage of surfactant at the alveolar level. This deficit of surfactant leads to an increase in alveolar surface tension that increases the retraction forces of the lung, leading to end-expiratory alveolar collapse, finally resulting in respiratory dysfunction, which includes hypoxemia, low lung compliance, increase of intrapulmonary shunts, low functional residual capacity, atelectasis, and pulmonary edema. The goal of the treatment and prevention of acute respiratory failure is therefore based on the following three main items: re-opening the collapsed alveolar units; preserving the active surfactant component in the remaining functional alveolar units, and preventing end-expiratory collapse. The following strategies can be used to prevent and/or treat acute respiratory failure: counterbalancing the retraction forces of the lung by applying sufficiently high external pressures; and/or decreasing the surface tension at the air-liquid interface by means of exogenous surfactant, and/or eliminating the air-liquid interface by filling the lung with perfluorocarbons. By applying these therapeutic strategies in routine clinical practice, we should achieve a reduction in the mortality rate of patients suffering from acute respiratory failure.

Key Words: Acute respiratory failure, Mechanical ventilation, Ventilation-induced lung injury, Surfactant therapy, Perfluorocarbons, Partial liquid ventilation.

Introduction

Acute respiratory failure (ARF) is still one of the most common reasons for admission to the intensive care unit (ICU). It is caused by many factors (1) and its incidence is approximately 77.6 patients per 100,000/year, with a 90-day mortality of 41% (2). In all cases of ARF, a pathologic shortage of surfactant at the alveolar level is observed (3). This deficit of surfactant increases alveolar surface tension, promoting end-expiratory instability with alveolar collapse and respiratory dysfunction, which includes hypoxemia and decreased lung compliance (4,5). It is clear that the more alveolar units are depleted of active surfactant aggregates, the more alveolar units will collapse and the more severe the respiratory failure will be (6–11). Based on this pathophysiological process, treatment of ARF should be based on preserving the active surfactant aggregates in the remaining functional alveolar units, re-opening collapsed alveolar units, and restoring end-expiratory alveolar stability from these surfactant-deficient alveoli (12–14). At present, it is thought that exogenous surfactant therapy, mechanical ventilation with positive pressure ventilation, and perfluorocarbon therapy might play an important role in modifying the disease process of ARF (12–17).

Physiology

Endogenous surfactant system. The integrity of the surfactant system of the lung is a prerequisite for normal breathing with the least possible effort (15). LaPlace, a French mathematician (1749–1827), was the first to draw attention to surface active forces in general, and described the relationship between force, surface tension, and radius of an air-liquid interface of a bubble as follows:

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$P = 2\gamma/r$ (P = pressure to stabilize a bubble; γ = surface tension at air-liquid interface, and r = radius of a bubble).

Nearly one century later, von Neergaard applied this law to pulmonary alveoli by demonstrating that the pressures required to expand an air-filled lung were nearly three times those required to distend a lung filled with fluid (18). In this manner, the surface tension effect at the air-liquid boundary was eliminated (Figure 1). From these findings, he concluded that 1) two-thirds of the retractile forces in the lung are due to surface tension phenomenon that act at the air-liquid interface of the alveoli, and 2) the surface tension at the air-liquid interface must be reduced by the presence of a surface active material with a low surface tension to allow normal breathing (18). Surfactant is synthesized by the alveolar type II cells and secreted into alveolar spaces and small airways, lowering its surface tension (15). Pulmonary surfactant is a complex of phospholipids (80–90%), neutral lipids (5–10%), and at least four specific surfactant-proteins (5–10%) (including SP-A, SP-B, SP-C, and SP-D) lying as a layer at the air-liquid interface in the lung (19,20).

The normal physiological functions of the pulmonary surfactant system include the following (21):

a) Mechanical stabilization of lung alveoli. The surfactant system acts by decreasing surface tension of the interface between alveoli and air. During deflation of the lung, a static high surface tension would tend to promote alveolar collapse. However, as alveolar size decreases, pulmonary surfactant ensures that surface tension falls to approximately zero. Thus, at small alveolar volumes surface tension becomes a negligible force and thereby tends to promote alveolar stability (22).

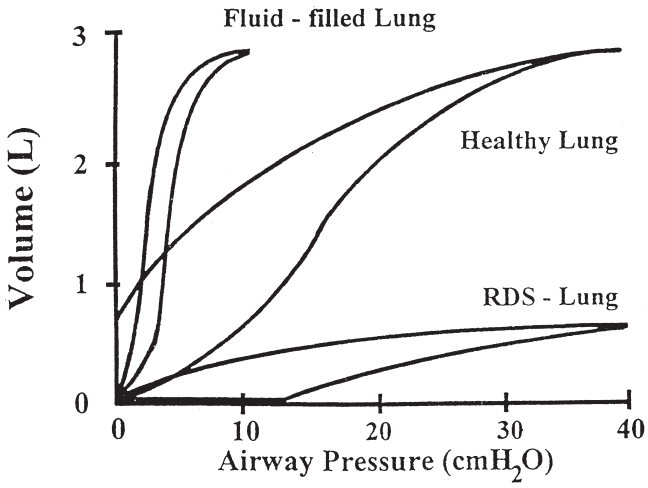

Figure 1. Pressure-volume diagrams of a normal air-filled lung and an ARDS lung. Von Neergaard showed in 1929 that much larger pressures were required to expand an air-filled lung than a lung filled with fluid. In a lung suffering from surfactant deficiency (RDS-Lung), even higher pressures are required to expand the lung, due to the high surface tension at the air–liquid interface in the alveoli caused by a diminished surfactant system (18).

b) Protection against lung edema. Another function of the pulmonary surfactant system is stabilization of the fluid balance in the lung and protection against lung edema (Figure 2). In general, alveolar flooding will not occur as long as the suction force in the pulmonary interstitium exceeds the pressure gradient generated by the surface tension in the alveolar air-liquid interface. Because this pressure gradient is inversely related to the radius of the alveolar curvature, there is for each combination of interstitial resorptive force and average surface tension a critical value for surface tension and for alveolar radius below which alveolar flooding occurs (23).

c) Surfactant and airway stabilization. As early as 1970, Macklem et al. (24) called attention to the significance of bronchial surfactant for stabilization of peripheral airways and hinted that lack of stabilization may cause airway obstruction or collapse of the small bronchi with air trapping. This has been proven in an animal model in which the bronchial surfactant was selectively destroyed (25). It was demonstrated that the pressure to open the collapsed bronchi is 20 cm H_2O. In addition to its role in mechanical stabilization, bronchial surfactant also has a transport function for mucus and inhaled particles (25). This has been proven *in vitro*, in a study showing that particles on a surface film move in one direction only if the surface film is compressed and dilated, comparable to compression and expansion during expiration and inspiration (25). Furthermore, bronchial surfactant also acts as an antiglue factor preventing the development of large adhesive forces between mucus particles, as well as between mucus and the bronchial wall (26).

d) Surfactant and local defense mechanisms. The surfactant system plays a role in the lung's defense against infection (27). Surfactant—in particular SP-A—enhances the antibacterial and antiviral defense of alveolar macrophages (27). It has been shown that the surfactant system may also be involved in protecting the lung against its own mediators (e.g., angiotensin II) and in protecting the cardiocirculatory system against mediators produced by the lung (28,29).

Disturbance of the surfactant system. Disturbance of the surfactant system can result from different factors (5). Damage to the alveolar-capillary membrane leads to high-permeability edema with wash-out or dilution of the surfactant and/or inactivation of the surfactant by plasma components, such as fibrin, albumin, globulin and transferrin, hemoglobin, and cell membrane lipids (30,31). These components are known to inhibit pulmonary surfactant function in a dose-dependent fashion (31). Furthermore, the pulmonary surfactant may also be disturbed by the following mechanisms: breakdown of surfactant by lipases and proteases;

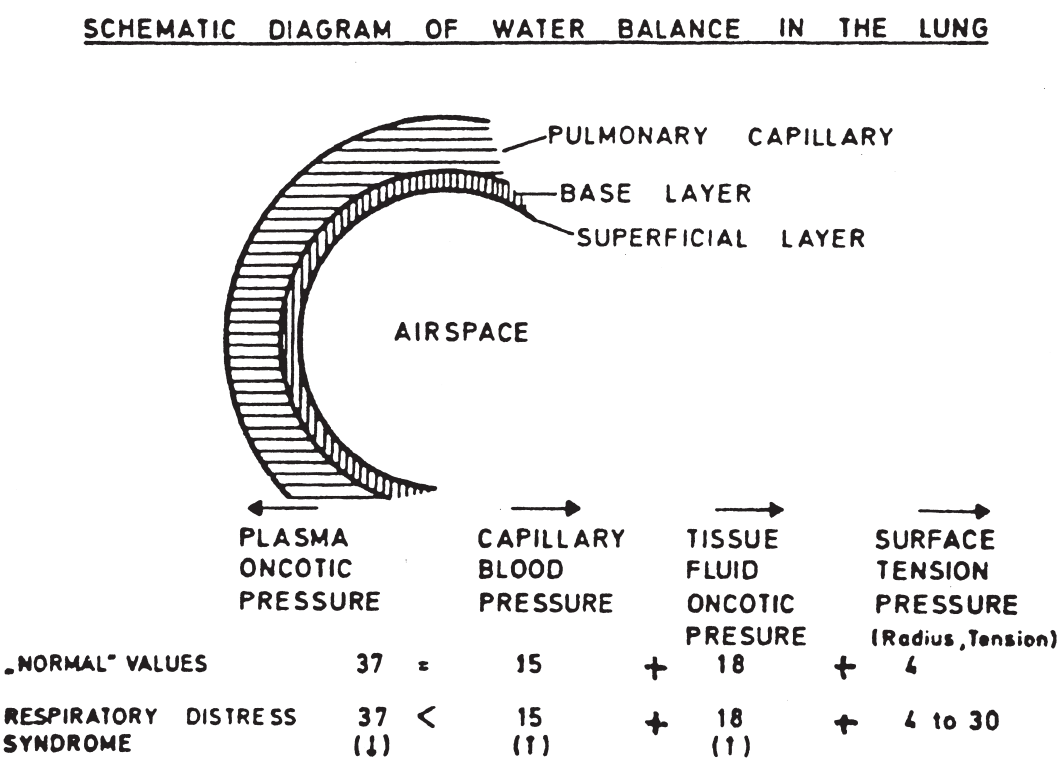

Figure 2. Simplified schematic diagram representing the factors influencing fluid balance in the lung (from Reference 33).

phospholipid peroxidation by free radicals; loss of surfactant from the airways due to mechanical ventilation with large tidal volumes; disturbed synthesis storage, or release of surfactant secondary to direct injury to type II cells (32).

Diminished pulmonary surfactant has far-reaching consequences for lung function. Independent of the cause, decreased surfactant function will directly or indirectly lead to the following:

1. Decreased pulmonary compliance
2. Decreased functional residual capacity
3. Atelectasis and enlargement of the functional right-to-left shunt
4. Decreased gas exchange and respiratory acidosis
5. Hypoxemia with anaerobic metabolism and metabolic acidosis
6. Pulmonary edema with further inactivation of surfactant by plasma constituents (33).

Mechanical Ventilation in the Treatment of ARF

Mechanical ventilation has been used for over 40 years to overcome the hypoxemia and low compliance produced during ARF. However, it has been shown that mechanical ventilation can damage the lungs when a mode of ventilation that allowed high inspiratory lung volumes and low levels of positive end-expiratory pressure (PEEP) is applied (6–11,34–36). In 1967, Ashbaugh and colleagues discussed the inactivation of the surfactant system by intra-alveolar plasma proteins in patients suffering from acute respiratory distress syndrome (37); since then, several studies have demonstrated qualitative and quantitative changes of surfactant in bronchoalveolar lavage fluid from patients with ARF (38–40). Gregory et al. (41) showed that minimal surface tension, total phospholipids, and surfactant proteins (SP-A and SP-B) were all decreased in bronchoalveolar lavage fluid obtained from patients suffering from ARF. In addition, this group observed that several of these alterations also occur in patients at risk for developing ARF, suggesting that these abnormalities of surfactant occur early in the disease process. Therefore, in experimental animals and patients suffering from ARF, lung damage is produced on the one hand by certain modes of mechanical ventilation and on the other by the disease process, unless a protective ventilatory strategy is used.

Surfactant changes during mechanical ventilation Studies have shown that during artificial ventilation, several mechanisms are involved in alterations of the surfactant function: 1) loss of surfactant into the small airways; 2) conversion of active large into non-active small surfactant aggregates, and 3) inactivation of the alveolar lining layer due to edema fluid.

Mechanical ventilation enhances the release of surfactant from type II pneumocytes into the alveoli by a metaboli-

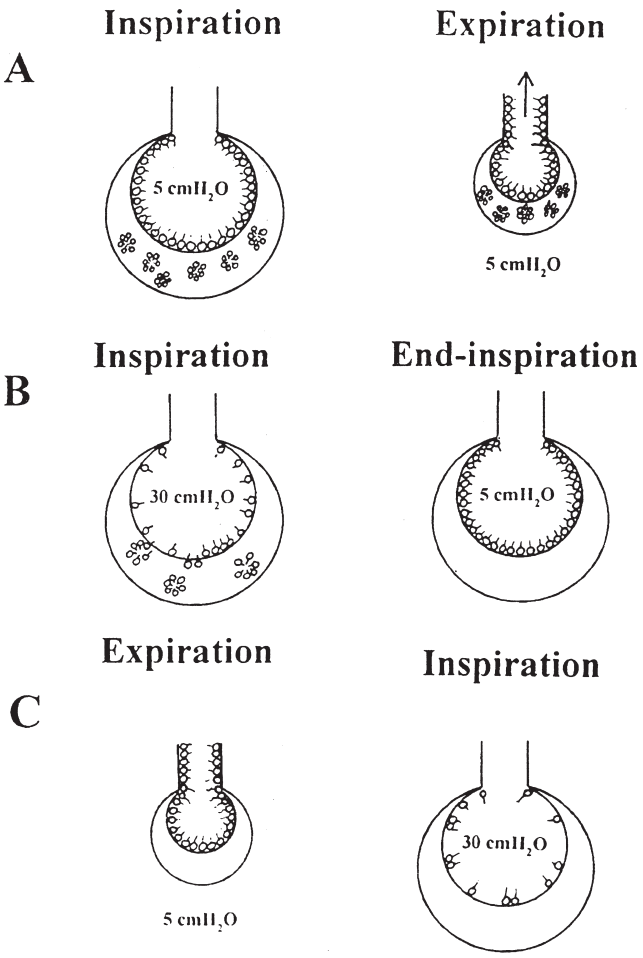

Figure 3. A) Balance between synthesis, release, and consumption of surfactant in the healthy lung. The pressure values given represent the intrapulmonary pressure needed to open the alveolus. At the surface and the hypophase (micelles), there are sufficient molecules of surfactant. These micelles deliver the surfactant necessary to replace the molecules squeezed out during expiration; B) Imbalance between synthesis, release, and consumption of surfactant due to artificial ventilation. At the beginning of inspiration, there is an apparent deficiency of surfactant molecules, but there is a respreading of molecules stored in the hypophase of the surfactant layer. At the end of inspiration there is, in principle, enough surfactant on the surface; C) With the next expiration, surface active molecules are squeezed out and no surface active molecules remain in the hypophase for respreading, creating a situation in which a serious surfactant deficiency follows (from Reference 13).

cally active process (6–10). This released material is squeezed from the alveoli into the airways due to a compression of the surfactant film at end-expiration if the surface area of the alveolus becomes smaller than the surface occupied by the surfactant molecules (13). During the inflation that follows, the lost molecules are replaced by surfactant stored within the alveolus (hypophase) and the cells. More surfactant molecules are lost during the next expiration in an ongoing cycle (Figure 3). Studies by Veldhuizen et al. showed that the pulmonary surfactant can be subdivided into two distinct subfractions, i.e., 1) large surface-active aggregates that are the precursor for 2) the small aggregates with poor surface activity (42). *In vivo* and *in vitro* studies have shown that size of tidal volume correlates with magnitude of conversion from large active to small inactive subfractions (43). Therefore, ventilation with large tidal volume promotes inactivation of the pulmonary surfactant system.

It has been proven that loss of active molecules of surfactant with increase in alveolar surface tension results in a decrease in pericapillary pressure and an increase in permeability of the alveolo-capillary barrier to small solutes (44–47), indicating that surfactant has a primary role in regulation of permeability of the alveolo-capillary barrier to small solutes and proteins. Additionally, mechanical ventilation can disturb the functional integrity of the endothelium and epithelium, creating an imbalance at the alveolo-capillary membrane. Both increased capillary filtration pressure and altered microvascular protein permeability have been shown to contribute to pulmonary edema after lung overinflation.

Role of pressure and volume in ventilation-induced lung injury. Studies with high peak inspiratory pressure ventilation in which peak inspiratory lung volume was limited by thorax restriction have suggested that end-inspiratory lung volume, and not end-inspiratory pressure, is the main determinant of ventilation-induced lung injury (VILI) (48,49). However, alveolar pressure alone, as measured in such studies, does not provide a measure of alveolar distension. Rather than absolute airway pressure, absolute transpulmonary pressure (equal to alveolar pressure minus pleural pressure) is responsible for injury. Therefore, at a given lung-thoracic compliance absolute transpulmonary pressure and end-inspiratory lung volume are interchangeable and indistinguishable with respect to their injurious potential.

It is known that greater than the endothelium or interstitial spaces, the epithelium is rate-limiting for solute and fluid movement between blood and alveolus (50,51). Effects of overinflation on epithelial permeability have been studied in fluid-filled, *in situ* lobes to exclude the effect of surface tension. As the epithelium is progressively stretched during static inflation, there is a non-reversible opening of water-filled channels between alveolar cells resulting in free diffusion of small solutes and even albumin across the epithelial barrier (52–54). Such changes were shown to occur only at high distending pressures and have been attributed to peak inspiratory epithelial overstretching, which occurs due to inflation solely in the supra-physiological range (54–56). Due to damage to both the epithelial and endothelial barrier, surfactant components may be lost into the bloodstream (55). More importantly, protein will accumulate intra-alveolarly, which results in a dose-dependent inhibition of surfactant (31). As surfactant is rate-limiting for transfer of proteins over the alveolo-capillary barrier, loss of surfac-

tant function will lead to further protein infiltration. This may result in a self-triggering mechanism of surfactant inactivation (31,57–59).

Structural damage of the alveolo-capillary barrier due to repeated collapse and re-expansion of alveoli. Pioneering work of Mead and colleagues (60) demonstrated that due to the pulmonary interdependence of the alveoli, the forces acting upon the fragile lung tissue in non-uniformly expanded lungs are not only the applied transpulmonary pressures but also the shear forces present in the interstitium between open and closed alveoli (Figure 4). An alveolus with surfactant impairment would be predisposed to end-expiratory alveolar collapse and prone to be affected by such shear forces. Shear forces rather than end-inspiratory overstretching may well be the major reason for epithelial disruption, loss of barrier function of the alveolar epithelium, and considerable increases in regional microvascular transmural pressure.

Important evidence for this mechanism proceeds from the finding that ventilation at low lung volumes can also augment lung injury in lungs with an impaired surfactant system (61). A recent study in a model of subtle surfactant perturbation by dioctyl sodium sulfosuccionate showed that surfactant changes render the lung vulnerable to lung parenchymal injury by mechanical ventilation (62). These studies confirm the earlier work of Nilsson et al. (63) in ventilated newborn premature rabbits with a primary surfactant deficiency. Fetuses treated with surfactant prior to receiving mechanical ventilation had fewer bronchiolar epithelial lesions in comparison with nonsurfactant-treated controls.

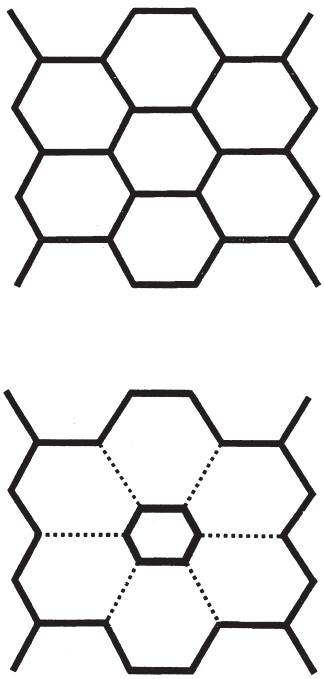

Figure 4. Shear forces are caused between open and closed alveoli due to pulmonary interdependence of alveoli. This figure shows the difference between mechanical ventilation of normal alveoli (upper panel) and mechanical ventilation of the same alveolar unit after surfactant inactivation (lower panel), which results in end-expiratory collapse (adapted from Reference 60).

Improvement of gas exchange, lung function, and permeability changes by positive end-expiratory pressure (PEEP) during mechanical ventilation. Initial studies have investigated the effect of increasing levels of PEEP at constant tidal volume ventilation, which resulted in higher end-inspiratory pressures and volumes. Such studies found that increasing levels of PEEP reduced shunt (64–66) and improved oxygenation and lung mechanics attributed to reopening of flooded alveoli with redistribution of edema fluid from flooded alveoli into the interstitial spaces (67–69). Such studies, however, also demonstrated that the use of high PEEP levels did not reduce (64,66,70) or even increase edema formation (65,71). These findings have been reported in both isolated perfused lungs (64) and in closed-chest healthy animals (66) and closed-chest animals with different forms of lung injury induced by bronchial hydrochloric acid administration (67), alloxan (70), oleic acid (72), or hydrostatic edema due to lobar venous occlusion (71). Overinflation due to PEEP is probably the explanation for the lack of reduction or even worsening of edema reported with PEEP during such experiments (73). However, it has now been demonstrated in different animal models that ventilation with PEEP at lower tidal volumes results in less edema than ventilation without PEEP and higher tidal volume for the same peak or mean airway pressure (34,73,74); additionally, it has been demonstrated more specifically that PEEP prevents alveolar flooding (34,36,75). Dreyfuss et al. showed in rats ventilated at peak inspiratory pressure of 45 cm H_2O that damage due to mechanical ventilation begins at the endothelial side after 5 min and rapidly progresses to the epithelium after 20 min (35). A subsequent study showed a reduction of endothelial injury and preservation of the structure of the alveolar epithelium by use of 10 cm H_2O of PEEP, which was accompanied by a lack of alveolar flooding (49). Experiments in the same rat model of overinflation showed a significant conversion of active into non-active surfactant aggregates compared to non-ventilated controls after lung overinflation; 10 cm H_2O PEEP was shown to prevent a significant conversion of large aggregates into small aggregates compared with non-ventilated controls (36). The latter study suggests that the beneficial effect of PEEP in reducing protein infiltration after overinflation at peak inspiratory pressure of 45 cm H_2O without PEEP in rats is partially attributed to reduced filtration by surfactant preservation (36).

Two basic mechanisms have been described in the literature explaining the surfactant-preserving effect of PEEP during mechanical ventilation. Studies by Wyszogrodski et al. have shown that PEEP prevents a decrease in lung compliance and surface activity of lung extracts, indicating a

prevention of loss of alveolar surfactant function during lung overinflation (10). Others have suggested that PEEP prevents alveolar collapse and thus maintains the end-expiratory volume of alveoli at a higher level, thereby preventing excessive loss of surfactant in the small airways by a squeeze-out mechanism during expiration (75–77). The utilization of PEEP to splint open airways and alveoli at end-expiration in surfactant-deficient lungs may markedly reduce lung injury. Studies in both saline-lavage isolated perfused rat lungs (61) and saline-lavage intact animals (78,79) have shown that ventilation strategies maintaining the alveoli open throughout the respiratory cycle via sufficiently high levels of PEEP induce significantly less morphological injury with better preservation of pulmonary compliance than strategies in which alveolar collapse is allowed to occur at end-expiration. Although healthy lungs do not appear to be damaged when terminal units are repeatedly opened or closed for short periods by negative end-expiratory pressure (that nevertheless reduces compliance and alters gas exchange), it does become clear from what was previously discussed that early surfactant changes, which may be induced by mechanical ventilation itself, predispose lungs for VILI by repeated opening and closure of alveolar units (62).

Techniques to Protect the Lung During Mechanical Ventilation in ARF

The consequence of high alveolar surface tension is end-expiratory alveolar instability and alveolar collapse. It has been shown that in ARF, atelectatic lung areas are mainly distributed in the dependent lung regions (vertebral regions), while in the anterior or non-dependent regions the lung is mainly composed of open healthy alveoli (80). Depending on the magnitude of lung damage, the proportion of alveoli that can consequently be ventilated may be reduced to nearly 20–30% of a normal lung. Gattinoni et al. showed that patients with early ARF and collapsed dependent lung regions have a reduced volume of aerated lung (80). Volume-controlled mechanical ventilation will predominantly ventilate this aerated healthy portion of the lung with overdistension in such regions. If one assumes that 75% of the lung is consolidated and only 25% ventilated, then small tidal volume ventilation, e.g., 7 mL/kg body weight, would result in tidal volumes of 28 mL/kg in such lung regions with a danger of overdistension and further lung impairment. Use of pressure-controlled, time-cycled modes of ventilation in which alveolar pressure can never exceed the peak inspiratory pressure set on the ventilator is then preferable to reduce dangerous alveolar overdistension in these lung areas (5).

With the intention of protecting the lung against VILI, an international consensus conference compiled the following recommendations: plateau pressure should be limited to 35 cm H_2O; tidal volume should be as low as 5 mL/kg; permissive hypercapnia was allowed if normocapnia is not achievable at a limited plateau pressure, and FiO_2 should be minimized. In addition, a re-expansion maneuver should be performed (81). It was suggested that to prevent overdistension in ARF patients, tidal volumes must be decreased (82), and that tidal volume reduction would increase oxygen delivery due to better hemodynamics (83,84).

Preliminary reports of reduced tidal volumes by end-inspiratory airway pressure limitation in patients with or at risk of ARF, however, showed no reduction in mortality rate (85–87). Such findings may be explained by a certain degree of VILI even with small tidal volume ventilation, due to repeated alveolar collapse and re-expansion. Lachmann et al. proposed that a protective ventilatory strategy based on the law of LaPlace should be used (5,13). They showed that raising airway pressures higher than 40 cm H_2O resulted in a recruitment of most functional alveolar units. Once opened, these units should be maintained open by the minimal PEEP level; gas exchange can be maintained in the normal range even at low pressure amplitude between PIP and PEEP. These low-pressure amplitudes produce fewer shear forces and thus protect against VILI. However, only a few clinical studies have been performed using this ventilatory strategy (5,88), which produces a ventilatory condition that saves the lung from further damage, allows reduction of FiO_2, promotes resorption of interstitial and intrapulmonary edema, and finally reduces pulmonary artery pressures by overcoming hypoxic pulmonary vasoconstriction (5). A similar protective ventilatory strategy can be applied using high frequency oscillatory ventilation (HFOV) at high levels of mean airway pressure, which results in low oscillation pressure amplitude, low tidal volumes, and normal values of carbon dioxide ($PaCO_2$) (89,90).

Froese's group showed that HFOV is useful to protect the lung, but only after a re-expansion maneuver; the oscillation pressure amplitude itself is adjusted according to $PaCO_2$ values (89). The ease of this intervention renders this strategy a standard of ventilation in some neonatal intensive care units. However, its usefulness has been questioned by multicenter studies in which no initial re-expansion maneuver was performed, showing no significant differences between HFOV and conventional mechanical ventilation (91). Additionally, our group showed in an experimental study that using the same ventilatory strategy, a conventional ventilator is as effective as a high frequency oscillatory ventilator in improving gas exchange and lung mechanics (92) and in preserving exogenous surfactant function (unpublished data).

Exogenous surfactant therapy. Re-establishing a physiological surface tension at the air-liquid interface by application of exogenous surfactant during mechanical ventilation will prevent end-expiratory collapse and dangerous shear forces between open and closed alveoli, resulting in improvement of blood oxygenation at lower fractions of in-

spired oxygen, use of lower airway pressures with reduced barotrauma, and improvement of survival (93). Clinical experience of surfactant therapy in neonates with respiratory distress syndrome (neonatal RDS) has shown that the response after exogenous surfactant therapy depends not only on the course of the injury, but also on the timing of surfactant therapy, the dose of exogenous surfactant used, the type of surfactant preparation, and the ventilator settings of the mechanical ventilation. In particular, the level of PEEP used and the method of administration of exogenous surfactant (important for the distribution of the instilled surfactant) play an important role (93).

The exact amount of exogenous surfactant required in ARF to restore lung surfactant function is not known, but different case reports and pilot studies suggest that a dose between 50 and 400 mg/kg body weight may be appropriate. Because the quantity of inhibitors differs from patient to patient, an excess of surfactant should always be administered or repeatedly substituted until blood gas values improve (94). Experience in neonates has also demonstrated that exogenous surfactant is more effective when administration takes place in the early stages of neonatal RDS (94). Early treatment of ARF may thus require smaller amounts of surfactant and outcome results will probably be better.

The currently used technique of delivering exogenous surfactant is bolus instillation through the endotracheal tube. This method has been used in most animal studies as well as in neonates who suffer from neonatal RDS due to primary surfactant deficiency (95). The advantage of this method of instillation is that it is rapid and able to deliver large quantities of surfactant. From animal studies and in studies of neonates suffering from RDS, it has been demonstrated that natural surfactant preparations are more effective in improving lung function immediately after instillation than artificial surfactant preparations, due to the lack of surfactant proteins (95,96). Also, different studies have demonstrated that surfactant proteins reduce the surfactant inactivation that may be caused by plasma constituents, which is of special importance in ARF. It has been shown that ventilator pattern strongly influences exogenous surfactant therapy (97,98). Several studies have demonstrated that surfactant therapy and positive end-expiratory pressure (PEEP) ventilation produce the largest and most sustained therapeutic effect (99,100). Surfactant administration does not permit immediate withdrawal of PEEP, but it is usually possible to reduce peak inspiratory pressures as lung function improves. This avoids overdistension of the alveoli and increased perfusion of the lung. It also reduces the number of pneumothoraces (101).

High frequency oscillation studies have shown that ventilation at high end-expiratory lung volumes combined with small volume cycles at high rates best preserves exogenous surfactant and gas exchange in lavaged lungs (100). However, to date only a few studies have been published on the combined use of surfactant and HFOV in animals or humans (91,92,102–104). It was shown that after surfactant therapy HFOV was superior to CMV in improving pulmonary function and reducing lung injury (91,98,102–103). In these studies, however, HFOV was used in combination with the high-lung volume strategy whereas CMV was not. Froese and colleagues (98) compared HFOV to CMV after surfactant therapy at low- and high-lung volume and confirmed that HFOV at high-lung volume was superior to the alternatives in improving gas exchange and lung mechanics in lung-lavaged rabbits. Surprisingly, these authors were unable to maintain oxygenation above 350 mmHg (according to the high-lung volume strategy) in the CMV group after surfactant therapy (98). This is in contrast to earlier results of CMV with surfactant therapy in lung-lavaged rabbits in which oxygenation rapidly increased to prelavage values after surfactant instillation and remained stable for 4 h (104,105). Froese et al. (98) demonstrated that the effect of exogenous surfactant on arterial oxygenation remained stable with HFOV, whereas it decreased significantly during the 4-h study period with CMV at high-lung volume. In this study, however, the high-lung volume strategy with CMV was performed by a gradual increase of PIP and PEEP but without an active volume recruitment maneuver, as used with HFOV. Furthermore, CMV was used with constant flow and high tidal volume (20 mL/kg), known to increase conversion from active into non-active surfactant subfractions; this leads to a shortage of active surfactant at the alveolar level. A recent study by our group (99) has shown that exogenous surfactant therapy can also be optimized by conventional pressure-controlled mechanical ventilation with small pressure amplitudes and high levels of end-expiratory pressure, as it can with high frequency oscillation. These settings resulted in optimal gas exchange and low levels of protein infiltration with minimal loss of active surfactant subfractions. Therefore, this ventilatory strategy can be directly compared with HFOV concerning the efficacy of exogenous surfactant therapy.

Partial liquid ventilation. An alternative technique to maintain end-expiratory stability consists of instilling perfluorocarbon fluids (PFC) into the lung. Because PFCs dissolve high amounts of oxygen and carbon dioxide at normospheric pressures, gas exchange over the alveolar air-liquid interface is maintained when conventional mechanical gas ventilation is superimposed. This technique has become known as partial liquid ventilation (PLV) (106–110). The hypothetical mechanism of PLV is explained in Figure 5; panel A shows the atelectatic ARF lung. After a small dose of PFC (3 mL/kg) a thin film with low surface tension is formed at the air-liquid interface due to evaporation of the PFC (panel B) and covers the lung units of the entire lung. Due to this film, increased surface tension in the diseased lung is reduced to a low and constant value, which leads to a decrease of inflation pressure; however, this pressure cannot further decrease with additional doses of PFC.

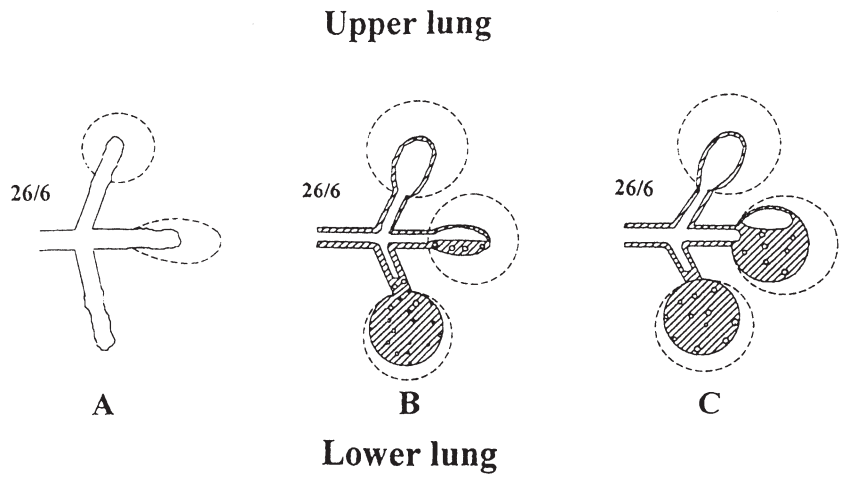

Figure 5. Panel A shows the atelectatic surfactant-deficient alveoli at end-inspiration (dashed line) and end-expiration (solid line). Panel B shows what occurs when PFC is instilled into the lung. Due to its evaporation, a thin layer of PFC is formed at the air-liquid interface and due to its low surface tension pulmonary compliance is improved. This already occurs at low-dose PFC and does not further improve with higher PFC dosing. Some dependent alveoli are prevented from end-expiratory collapse by the non-compressible PFC; this improves oxygenation. Panel C shows what occurs if more PFC is instilled into the lung: more alveoli are recruited at end-expiration. Therefore, there is a dose-dependent improvement in oxygenation with PFC during partial liquid ventilation (from Reference 14).

Independent of this speculation, dose-dependent improvement in oxygenation results from the filling of the collapsed atelectatic alveoli in the dependent part of the lung by the non-compressible PFC, thus preventing them from end-expiratory collapse (panel B vs. C). This leads to a continuation of gas exchange even during the expiratory phase of the respiratory cycle. With increasing amounts of PFC in the lung, more collapsed atelectatic alveoli can be opened and prevented from end-expiratory collapse, thus eliminating intrapulmonary shunt. This mechanism was recently supported by computed tomographic (CT) scans from Quintel et al. (111), who showed that during PLV PFC is distributed predominantly to the lower lung regions, whereas gas ventilation took place in the upper regions.

Our group was the first to apply this technique in animals suffering from acute respiratory failure (106–109), and showed the following: 1) higher doses of PFC lead to higher levels of oxygenation (106). This is suggested to result from dose-dependent recruitment of collapsed atelectatic alveoli by PFC fluid; 2) oxygenation deteriorates over time if no additional doses of PFC are applied (107). This is attributed to evaporation of PFC, which will cause affected alveoli to collapse; 3) lung mechanics and carbon dioxide elimination improve after an initial low dose of PFC and show no further improvements with subsequent higher doses of PFC (106). This is attributed to the replacement of the alveolar air-liquid interface with a thin air-PFC interface. Evaporating PFC appears to cover the entire lung surface. As PFCs have a low constant surface tension (=18 mN/m), pulmonary compliance is increased after low-dose PFC and CO_2 elimination is higher. No further improvement is seen after additional PFC dosing; 4) PLV does not impair any cardiovascular parameter, even in animals with a large anterior-posterior thoracic diameter. Mean pulmonary artery pressure decreases when PFC is applied, due to reversal of hypoxic pulmonary vasoconstriction (108); 5) PLV does prevent the progress of histologically assessed lung injury (106–110). External PEEP must be applied during PLV to prevent bulk movement of PFC fluids from the alveoli into the airways and to prevent dangerously high airway pressures at the onset of inspiration (106), and 6) PLV can be combined with other ventilatory support techniques in ARF (110).

Studies comparing PLV with exogenous surfactant therapy and high levels of PEEP should be performed. Additionally, due to the physical properties of perfluorocarbons PLV must be evaluated on the capability to restore lung function after ventilation-induced lung injury.

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References

1. Spragg RG, Smith RM. Biology of acute lung injury. In: Crystal RG, West JB, editors. The lung. New York: Scientific Foundations. Raven Press;1991. p. 2003.
2. Luhr OR, Antonsen K, Karlsson M, Aardal S, Thorsteinsson A, Frostell C, Bonde J, and the ARF Study Group. Incidence and mortality after acute respiratory failure and acute respiratory distress syndrome in Sweden, Denmark, and Iceland. Am J Respir Crit Care Med 1999;159:1849.
3. Lewis JF, Jobe AH. Surfactant and the adult respiratory distress syndrome. Am Rev Resp Dis 1993;147:218.
4. Verbrugge S, Lachmann B. Mechanisms of ventilation-induced lung

injury and its prevention: role of surfactant. Appl Cardiopulm Pathophysiol 1998;7:173.
5. Lachmann B, Danzmann E, Haendly B, Jonson B. Ventilator settings and gas exchange in respiratory distress syndrome: applied physiology in clinical respiratory care. In: Prakash O, editor. The Hague, The Netherlands: Nijhoff;1982. p. 141.
6. Mead J, Collier C. Relationship of volume history of lungs to respiratory mechanics in anesthetised dogs. J Appl Physiol 1959;14:669.
7. Faridy E, Permutt S, Riley R. Effect of ventilation on surface forces in excised dog's lungs. J Appl Physiol 1966;21:1453.
8. McClenahan J, Urtnowski A. Effect of ventilation on surfactant, and its turnover rate. J Appl Physiol 1967;23:215.
9. Forrest J. The effect of hyperventilation on pulmonary surface activity. Br J Anaesth 1972;44:313.
10. Wyszogrodski I, Kyei-Aboagye K, Taeush W, Avery E. Surfactant inactivation by hyperventilation: conservation by end-expiratory pressure. J Appl Physiol 1975;38:461.
11. Sykes MK. Does mechanical ventilation damage the lung? Acta Anaesthesiol Scand 1991;35(Suppl):126.
12. Lachmann B. Open up the lung and keep the lung open. Intensive Care Med 1992;118:319.
13. Houmes RJ, Bos JAH, Lachmann B. Effects of different ventilator settings on lung mechanics: with special reference to the surfactant system. Appl Cardiopulm Pathophysiol 1994;5:117.
14. Lachmann B, Gommers D, Govinda N. Rationale and techniques to improve ventilation and gas exchange in acute lung injury. J Jpn Med Soc Biol Interface 1996;26(Suppl):115.
15. Gommers D, Lachmann B. Surfactant therapy in the adult patient. Curr Opinion Crit Care 1995;1:57.
16. Lachmann B, Gommers D. Is it rational to treat pneumonia with exogenous surfactant? Eur Respir J 1993;6:1427.
17. Verbrugge SJC, Lachmann B. Partial liquid ventilation. Eur Respir J 1997;10:1937.
18. Von Neergaard K. Neue auffassungen über einen grundbegriff deer atemmechanik; die retraktionskraft deer lunge, abhängig von deer oberflächenspannung in den alveolen. Z Ges Exp Med 1929;66:3734.
19. Van Golde LMG, Batenburg JJ, Robertson B. The pulmonary surfactant system: biochemical aspects and functional significance. Physiol Rev 1988;68:374.
20. Johansson J, Curstedt T, Robertson B. The proteins of the surfactant system. Eur Respir J 1994;7:372.
21. Lachmann B, Danzmann E. Acute respiratory distress syndrome. In: Robertson B, van Golde LMG, Batenburg JJ, editors. Pulmonary surfactant. Amsterdam, The Netherlands: Elsevier;1984. p. 505.
22. Lachmann B, Winsel K, Reutgen H. Deer anti-atelectase faktor deer lunge I. Z Erkr Atm 1972;137:267.
23. Guyton AC, Moffatt DS, Adair TA. Role of alveolar surface tension in transepithelial movement of fluid. In: Robertson B, van Golde LMG, Batenburg JJ, editors. Pulmonary surfactant. Amsterdam, The Netherlands: Elsevier;1984. p. 171.
24. Macklem PT, Proctor DF, Hogg JC. The stability of peripheral airways. Resp Physiol 1970;8:191.
25. Lachmann B. Possible role of bronchial surfactant. Eur J Resp Dis 1985;67:49.
26. Reifenrath R. Surfactant action in bronchial mucus. In: Scarpelli EM, editor. Pulmonary surfactant system. Amsterdam, The Netherlands: Elsevier;1983. p. 339.
27. Van Iwaarden F. Surfactant and the pulmonary defense system. In: Robertson B, Van Golde LMG, Batenburg JJ, editors. Pulmonary surfactant. Amsterdam, The Netherlands: Elsevier;1992. p. 215.
28. Hein T, Lachmann B, Armbruster S, Smit JM, Voekel N, Erdmann W. Pulmonary surfactant inhibits the cardiovascular effects of platelet-activating factor (PAF), 5-hydroxytryptamine (5-HT) and angiotensin II. Am Rev Respir Dis 1987;135(Suppl):A506.
29. So KL, Gommers D, Lachmann B. Bronchoalveolar surfactant system and intratracheal adrenaline. Lancet 1993;341:120.
30. Seger W, Günther A, Walmrath HD, Grimminger F, Lasch HG. Alveolar surfactant and adult respiratory distress syndrome. Clin Investigator 1993;71:177.
31. Lachmann B, Eijking EP, So KL, Gommers D. *In vivo* evaluation of the inhibitory capacity of human plasma on exogenous surfactant function. Intensive Care Med 1994;20:6.
32. Stinson SF, Ryan DP, Hertwerk MS, Hardy JD, Hwang-Kow SY, Loosli CG. Epithelial and surfactant changes in influenza pulmonary lesions. Arch Pathol Lab Med 1976;100:147.
33. Lachmann B. The role of pulmonary surfactant in the pathogenesis and therapy of ARDS. In: Vincent JL, editor. Update in intensive care and emergency medicine. Berlin, Germany: Springer-Verlag;1987. p. 123.
34. 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.
35. Dreyfuss D, Basset G, Soler P, Saumon G. Intermittent positive pressure hyperventilation with high inflation pressures produces pulmonary microvascular injury in rats. Am Rev Respir Dis 1985;132:880.
36. Verbrugge SJC, Böhm SH, Gommers D, Zimmerman LJI, Lachmann B. Surfactant impairment after mechanical ventilation with large alveolar surface area changes and effects of positive end-expiratory pressure. Br J Anaesth 1998;80:1.
37. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. Lancet 1967;2:319.
38. Hallman M, Spragg R, Harrell JH, Moser KM, Gluck L. Evidence of lung function abnormality in respiratory failure. Study of bronchoalveolar lavage phospholipids, surface activity phospholipase activity, and plasma myoinositol. J Clin Invest 1982;70:673.
39. Pison U, Seeger W, Buchorn R, Joka T, Brand M, Obertacke U, Neuhof H, Schmit-Neuerburg KP. Surfactant abnormalities in patients with respiratory failure after multiple trauma. Am Rev Respir Dis 1989;140:1033.
40. Pison U, Obertacke U, Brand M. Altered pulmonary surfactant in uncomplicated and septicemia-complicated courses of acute respiratory failure. J Trauma 1991;30:19.
41. Gregory TJ, Longmore WJ, Moxley MA, Whitsett JA, Reed CR, Fowler AA, Hudson LD, Maunder RJ, Crim C, Hyers TM. Surfactant chemical composition and biophysical activity in acute respiratory distress syndrome. J Clin Invest 1991;88:1976.
42. Veldhuizen RAW, Marcou J, Yao LJ, McGraig L, Ito Y, Lewis JF. Alveolar surfactant aggregate conversion in ventilated normal and injured rabbits. Am J Physiol 1996;270:L152.
43. Ito Y, Veldhuizen RAW, Yao LJ, McGraig LA, Bartlett AJ, Lewis JF. Ventilation strategies affect surfactant aggregate conversion in acute lung injury. Am Rev Respir Crit Care Med 1997;155:493.
44. Pattle RE. Properties, function and origin of the alveolar lining layer. Nature 1955;175:1125.
45. Clements JA. Pulmonary edema and permeability of alveolar membranes. Arch Environ Health 1961;2:280.
46. Albert RK, Lakshminarayan S, Hildebrandt J, Kirk W, Butler L. Increased surface tension favors pulmonary edema formation in anaesthetized dogs' lungs. J Clin Invest 1979;63:1015.
47. Roedenberg CE, Nieman GF, Paskanik AM, Hart KE. Microvascular membrane permeability in high surface tension pulmonary edema. J Appl Physiol 1986;60:253.
48. Hernández LA, Peevy KJ, Moise AA, Parker JC. Chest wall restriction limits high airway pressure-induced lung injury in young rabbits. J Appl Physiol 1989;66:2364.
49. Dreyfuss D, Soler P, Basset G, Saumon G. High inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. Am Rev Resp Dis 1988;137:1159.
50. Gorin AB, Stewart PA. Differential permeability of endothelial and epithelial barriers to albumin flux. J Appl Physiol 1979;47:1315.

51. Effros RM, Mason GR, Raj JU. Effects of mechanical ventilation and barotrauma on pulmonary clearance of ^{99m}technetium diethylenetriamine pentaacetate in lambs. Pediatr Res 1990;27:100.
52. Egan EA, Nelson RM, Olver RE. Lung inflation and alveolar permeability to nonelectrolytes in adult sheep *in vivo*. J Physiol 1976; 260:409.
53. Ramanathan R, Mason GR, Raj JU. Effects of mechanical ventilation and barotrauma on pulmonary clearance of ^{99m}technetium diethylenetriamine pentaacetate in lambs. Pediatr Res 1990;27:70.
54. Kim KJ, Crandall ED. Effects of lung inflation on alveolar epithelial solute and water transport properties. J Appl Physiol 1982;52:1498.
55. Evander E, Wollmer P, Jonson B. Pulmonary clearance of inhaled ^{99}Tc-DPTA: effects of ventilation pattern. Clin Physiol 1990;10:189.
56. O'Brodovich H, Coates G, Marrin M. Effects of inspiratory resistance and PEEP on ^{99m}Tc-DPTA clearance. J Appl Physiol 1986; 60:1461.
57. Said SI, Avery ME, Davis RK, Banerjee CM, El-Cohary M. Pulmonary surface activity in induced pulmonary edema. J Clin Invest 1965;44:458.
58. Seeger W, Stör G, Wolf HRD, Neuhof H. Alteration of surfactant function due to protein leakage: special interaction with the fibrin monomer. J Appl Physiol 1985;58:326.
59. Kobayashi T, Nitta K, Ganzuka M, Inui S, Grossmann G, Robertson B. Inactivation of exogenous surfactant by pulmonary edema fluid. Pediatr Res 1991;29:353.
60. Mead J, Takishima T, Leith D. Stress distribution in lungs: a model of pulmonary elasticity. J Appl Physiol 1970;28:596.
61. Muscerede JG, Mullen JBM, Gan K, Slutsky AS. Tidal ventilation at low airway pressures can augment lung injury. Am J Respir Crit Care Med 1994;149:1327.
62. Taskar V, John E, Evander P, Robertson B, Jonson B. Surfactant dysfunction makes lungs vulnerable to repetitive collapse and reexpansion. Am J Respir Crit Care Med 1997;155:313.
63. Nilsson R, Grossman G, Robertson B. Pathogenesis of neonatal lung lesions induced by artificial ventilation: evidence against the role of barotrauma. Respiration 1980;40:218.
64. Caldini P, Leith JD. Brennan MJ. Effect of continuous positive-pressure ventilation (CPPV) on edema formation in dog lung. J Appl Physiol 1975;39:672.
65. Toung T, Saharia P, Permutt S, Zuidema GD, Cameron JL. Aspiration pneumonia: beneficial and harmful effects of positive end-expiratory pressure. Surgery 1997;82:279.
66. Hopewell PC, Murray JF. Effects of continuous positive pressure ventilation in experimental pulmonary edema. J Appl Physiol 1976; 40:568.
67. Permutt S. Mechanical influences on water accumulation in the lungs. In: Fishman AP, Renkin EM, editors. Pulmonary edema: clinical physiological series. Bethesda, MD, USA: American Physiological Society;1979. p. 175.
68. Peré PD, Warriner EM, Baile EM, Hogg JC. Redistribution of pulmonary extravascular water with positive end-expiratory pressure in canine pulmonary edema. Am Rev Resp Dis 1983;127:590.
69. Malo J, Ali J, Wood LDH. How does positive end-expiratory pressure reduce intrapulmonary shunt in canine pulmonary edema? J Appl Physiol 1984;57:1002.
70. Hopewell PC. Failure of positive end-expiratory pressure to decrease lung water content in alloxan-induced pulmonary edema. Am Rev Resp Dis 1979;120:813.
71. Demling RH, Staub NC, Edmunds LH Jr. Effect of end-expiratory airway pressure on accumulation of extravascular lung water. J Appl Physiol 1975;38:907.
72. Luce JM, Huan TW, Robertson HT, Colley PS, Gronka R, Nessly ML, Cheney FW. The effects of prophylactic expiratory positive airway pressure on the resolution of oleic acid-induced lung injury in dogs. Ann Surg 1983;197:327.
73. Bshouty Z, Ali J, Younes M. Effect of tidal volume and PEEP on rate of edema formation in *in situ* perfused canine lobes. J Appl Physiol 1988;64:1900.
74. Houmes RJM, Bos HAH, Lachmann B. Effect of different ventilator settings on lung mechanics with special reference to the surfactant system. Appl Cardiopulm Pathophysiol 1994;5:117.
75. Dreyfuss D, Saumon G. Ventilator induced lung injury. Lessons from experimental studies. Am Rev Respir Dis 1998;157:294.
76. Veldhuizen RAW, Marcou J, Yao LJ, McGraig L, Ito Y, Lewis JF. Alveolar surfactant aggregate conversion in ventilated normal and injured rabbits. Am J Physiol 1996;270:152.
77. Verbrugge SJC, Vazquez de Anda G, Gommers D, Neggers SJCMM, Sorm V, Böhm SH, Lachmann B. Exogenous surfactant preserves lung function and reduces alveolar Evans blue dye influx in a rat model of ventilation-induced lung injury. Anesthesiology 1998; 89:467.
78. Argiras EP, Blakeley CR, Dunnill MS, Otremski S, Sykes MK. High PEEP decreases hyaline membrane formation in surfactant deficient lungs. Br J Anaesth 1987;59:1278.
79. Sandhar BK, Niblett DJ, Argiras EP, Dunnill MS, Sykes MK. Effects of positive end-expiratory pressure on hyaline membrane formation in a rabbit model of the neonatal respiratory distress syndrome. Intensive Care Med 1998;14:538.
80. Gattinoni L, Pesenti A, Torresin A, Baglioni S, Rivolta M, Rossi F, Scarini F, Marcolin R, Cappelleti G. Adult respiratory distress syndrome profiles by computed tomography. J Thorac Imag 1986;1:25.
81. Slutsky A. Consensus conference on mechanical ventilation January 28–30, at Northbrook, IL, USA. Part 1. Intensive Care Med 1994; 29:64.
82. Roupie E, Dambrosio M, Servillo G, Mentec H, El Atrous S, Beydon L, Brun-Bruisson C, Lemaire F, Brochard L. Titration of tidal volume and induced hypercapnia in acute respiratory distress syndrome. Am J Resp Crit Care Med 1995;152:121.
83. Leatherman JW, Lari RL, Iber C, Ney AL. Tidal volume reduction in ARDS: effect on cardiac output and arterial oxygenation. Chest 1991;99:1227.
84. Kiiski R, Takala A, Kari A, Milic-Emili J. Effect of tidal volume on gas exchange and oxygen transport in the adult respiratory distress syndrome. Am Rev Resp Dis 1992;146:1131.
85. Brochard L, Roudot-Thoroval F. Tidal volume reduction in acute respiratory distress syndrome: a multicenter randomized study. Am J Resp Crit Care Med 1997;155:A505.
86. Brower R, Shanhotz C, Shade D, Fessler H, White P, Wiener C, Teeter J, Almog Y, Dodd-O J, Piantadosi S. Randomized controlled trial of small tidal volume ventilation in ARDS. Am J Resp Crit Care Med 1997;155:A93.
87. Stewart TE, Meade MO, Cook DJ, Granton JT, Hodder RV, Lapinsky SE, Mazer CD, McLean RF, Rogovein TS, Schouten BD, Todd TRJ, Slutsky AS. 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.
88. Amato MBP, Barbas CSV, Medeiros DM, Magaldi RB, Shettino GPP, Lorenzi Filho G, Kairalla RA, Deheinzelin D, Morais C, Fernandes EO, Takagaki TY, de Carvalho CRR. Beneficial effects of the "open lung approach" with low distending pressures in acute respiratory distress syndrome. Am J Respir Crit Care Med 1995; 152:1835.
89. Froese A, Bryan C. High frequency ventilation. Am Rev Respir Dis 1987;135:1363.
90. Froese A. High frequency oscillatory ventilation for adult respiratory distress syndrome: let's get it right this time. Crit Care Med 1997; 25:906.
91. Ogawa Y, Miyasaka K, Kawano T, Imura S, Inukai K, Okuyama K, Oguchi K, Togari N, Nishida H, Mishina J. A multicenter randomized trial of high frequency oscillatory ventilation as compared with conventional mechanical ventilation in preterm infants with respiratory failure. Early Hum Develop 1992;32:1.

92. Vazquez de Anda GF, Hartog A, Verbrugge SJC, Gommers D, Lachmann B. The open lung concept: pressure controlled ventilation is as effective as high frequency oscillatory ventilation in improving gas exchange and lung mechanics in surfactant-deficient animals. Intensive Care Med 1999;25:990.
93. Gommers D, Lachmann B. Surfactant therapy: does it have a role in adults? Clin Intensive Care 1993;4:284.
94. Jobe AH. Pulmonary surfactant therapy. N Engl J Med 1993;328:861.
95. Lewis JF, Tabor B, Ikegami, Jobe AH, Joseph M, Absolom D. Lung function and surfactant distribution in saline-lavaged sheep given instilled vs. nebulized surfactant. J Appl Physiol 1993;74:1256.
96. Gommers D, van't Veen A, Verbrugge SJC, Lachmann B. Comparison of eight different surfactant preparations on improvement of blood gases in lung-lavaged rats. Appl Cardiopulm Pathophysiol 1998;7:95.
97. Verbrugge SJC, Sorm V, Lachmann B. Mechanisms of acute respiratory distress syndrome: role of surfactant changes and mechanical ventilation. J Physiol Pharmacol 1997;48:537.
98. Froese AB, McCulloch PR, Sugiura M, Vaclavick S, Possmayer F, Moller F. Optimizing alveolar expansion prolongs the effectiveness of exogenous surfactant therapy in the adult rabbit. Am Rev Respir Dis 1993;148:569.
99. Verbrugge SJC, Gommers D, Lachmann B. Conventional ventilation modes with small pressure amplitudes and high end-expiratory pressure levels optimize surfactant therapy. Crit Care Med 1999;27:2724.
100. Hallman M, Merritt TA, Kari A. Factors affecting surfactant responsiveness. Ann Med 1991;23:693.
101. Gerstmann DR, Minton SD, Stoddard RA, Meredith KS, Monaco F, Betrand JM, Battisti O, Langhendries JP, Francois A, Clark RH. The PROVO multicenter early high-frequency oscillatory ventilation trial: improved pulmonary and clinical outcome in respiratory distress syndrome. Pediatrics 1996;98:1044.
102. Nilsson R, Berggren P, Curstedt T, Grossman G, Renheim G, Robertson B. Surfactant and ventilation by high frequency oscillation in premature newborn rabbits: effect on survival, lung aeration, and bronchiolar epithelial lesions. Pediatr Res 1985;19:143.
103. Jackson JC, Truog WE, Standeaert TA, Murphy JH, Juul SE, Chi EY, Hildebrandt J, Hodson WA. Reduction in lung injury after combined surfactant and high-frequency ventilation. Am J Respir Crit Care Med 1994;150:534.
104. Gommers D, Hartog A, Schnabel R, De Jaegere A, Lachmann B. High-frequency oscillatory ventilation is not superior to conventional mechanical ventilation in surfactant-treated rabbits with lung injury. Eur Respir J 1999;14:738.
105. Gommers D, Vilstrup C, Bos JAH, Larsson A, Werner O, Hannappel E, Lachmann B. Exogenous surfactant therapy increases static lung compliance, and cannot be assessed by measurements of dynamic compliance alone. Crit Care Med 1993;21:567.
106. Tütüncü AS, Faithfull S, Lachmann B. Intratracheal perfluorocarbon administration combined with mechanical ventilation in experimental respiratory distress syndrome: dose-dependent improvement of gas exchange. Crit Care Med 1993;21:962.
107. Tütüncü AS, Akpir K, Mulder P, Erdmann W, Lachmann B. Intratracheal perfluorocarbon administration as an aid in the ventilatory management of respiratory distress syndrome. Anesthesiology 1993;79:1083.
108. Houmes RJM, Verbrugge SJC, Hendrik ER, Lachmann B. Hemodynamic effects of partial liquid ventilation with perfluorocarbon in acute lung injury. Intensive Care Med 1995;21:966.
109. Houmes RJM, Hartog A, Verbrugge SJC, Böhm SH, Lachmann B. Combining partial liquid ventilation with nitric oxide to improve gas exchange in acute lung injury. Intensive Care Med 1997;23:162.
110. Hirschl RB, Parent RB, Tooley R. Liquid ventilation improves pulmonary function, gas exchange and lung injury in a model of respiratory failure. Ann Surg 1995;21:79.
111. Quintel M, Hirschl R, Roth H, Loose R, van Ackern K. Computer tomographic assessment of perfluorocarbon and gas distribution during partial liquid ventilation for acute respiratory failure. Am J Respir Crit Care Med 1998;158:249.