Ventilator-induced Lung Injury
Lessons from Experimental Studies

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INTRODUCTION: VENTILATOR-INDUCED LUNG INJURY: NOT ONLY AIR LEAKS

Mechanical ventilation has been used to support acutely ill patients for several decades. But clinicians are aware that, despite the life-saving potential of this assistance, it has several potential drawbacks and complications. A State of the Art review published several years ago in the *American Review of Respiratory Disease* recapitulated these complications (1). The present review focuses on what has recently emerged as one of the most serious potential complications of mechanical ventilation, ventilation-induced lung injury (VILI). VILI was, for years, synonymous with clinical barotrauma, the leakage of air due to disruption of the airspace wall. The extra-alveolar accumulation of air causes several manifestations (2), of which the most threatening is tension pneumothorax. The adverse consequences of these macroscopic events are usually immediately obvious, and this form of barotrauma has been the subject of clinical studies and the remarkable experimental studies of Macklin and Macklin (3). It is only very recently that the possibility that more subtle physiologic and morphologic alterations may occur during mechanical ventilation has been recognized. This form of injury is now a major preoccupation of most physicians caring for patients needing ventilatory support. Although several fundamental experimental studies were published before 1975, it was only 10 yr later that renewed interest in this subject stimulated the major research effort which has considerably expanded our knowledge. Unlike the classic forms of barotrauma (i.e., extra-alveolar air), our knowledge of these alterations has come only from experimental studies. Alterations in lung fluid balance, increases in endothelial and epithelial permeability, and severe tissue damage have been seen following mechanical ventilation in animals. The macroscopic and even microscopic damage observed in VILI (4–6) is not specific. It closely resembles that observed in other forms of experimental acute lung injury (7–9). More importantly, it does not fundamentally differ from the diffuse alveolar damage observed during human acute respiratory distress syndrome (10). Thus, were VILI to occur in humans, it would be indistinguishable from most of the initial acute offending processes that lead to respiratory failure and the need for ventilator assistance. The possibility that mechanical ventilation can actually worsen acute lung disease is now widely accepted (11), despite the lack of a clear demonstration of a clinical equivalent of the experimental observations. Any demonstration of superimposed VILI during the course of human acute respiratory distress syndrome may be illusive. Thus, this concept derived from animal studies has resulted in complete reassessment of the use of mechanical ventilation for patients with acute lung diseases and underlies current trends in the clinical practice of mechanical ventilation (12). Indeed, the current orientation is to emphasize the potential importance of easing the stress on acutely injured lungs by using modes of ventilation that limit the pressure and volume of gas delivered to the lungs (13–18).

VENTILATION-INDUCED PULMONARY EDEMA AND RELATED FINDINGS: A HISTORICAL PERSPECTIVE

The safety of mechanical ventilation for the treatment of patients with acute respiratory failure has been a matter of concern ever since its introduction into medical practice. Several early experimental and clinical studies suggested that mechanical ventilation may adversely affect the lungs. Greenfield and

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colleagues (19) ventilated closed-chest dogs for 2 h at 26–32 cm H_2O peak inspiratory pressure. The animals were then allowed to recover for 24 h before undergoing thoracotomy. Zones of atelectasis were found at gross examination and the extracts of these lungs had increased surface tension, suggesting altered surfactant properties.

A few years later, Sladen and colleagues (20) reported that patients ventilated for long periods suffered from deteriorated lung function, an increased alveolar–arterial oxygen gradient, and a fall in respiratory system quasi-static compliance. However, the potential harmful effects of mechanical ventilation remained controversial. In an experimental study published in 1971, Nash and colleagues (21) claimed that the term "respirator lung" was a misnomer. They subjected goats to intermittent positive pressure ventilation with 13 cm H_2O peak airway pressure, using either 100% fraction of inspired oxygen (FI_{O_2}) or room air as the inspired gas. The animals given 100% O_2 did not survive for more than 4 d. At autopsy, their lungs had severe edema and hyaline membranes. In contrast, animals ventilated with room air remained well for up to 2 wk and their lungs did not differ from control animals. The conclusion was that even prolonged mechanical ventilation does not cause lung damage. However, they rightly pointed out that they used physiologic, low peak inspiratory pressures. Subsequently, it was conclusively demonstrated that "respirator lung" is in fact a true morbid entity, especially when higher peak inspiratory pressures are used. Many studies have sought to identify risk factors, or the potential adverse effects of the various forms of mechanical ventilation, and to develop strategies for preventing VILI. The deleterious effects of mechanical ventilation depend on numerous factors, among which (as will be detailed in the following sections), the level of airway pressure applied and the resulting volume changes, animal size, duration of ventilation, and whether the thorax is open or closed are the most significant.

Webb and Tierney conducted the first comprehensive study in intact animals that unambiguously demonstrated that mechanical ventilation may produce pulmonary edema (22). They subjected rats to positive airway pressure ventilation with peak pressures of 14, 30, and 45 cm H_2O. No abnormality was observed after 1 h of ventilation with 14 cm H_2O peak pressure. However, pulmonary edema occurred when animals were ventilated with higher peak pressures. Edema developed more rapidly and was more severe in animals ventilated with 45 cm H_2O than in those ventilated with 30 cm H_2O peak pressure: moderate interstitial edema was found in animals ventilated for 60 min with 30 cm H_2O peak pressure, whereas profuse edema and alveolar flooding developed within 13 to 35 min in animals ventilated with 45 cm H_2O peak pressure. Other studies (4, 6) subsequently showed that mild interstital edema can be demonstrated after a few (2 to 5) minutes of ventilation in rats with such a high peak airway pressure. Replication of these observations in larger animals requires much longer periods of ventilation (23–27), for reasons that are not yet understood. The implications of these differences between large and small species will be discussed later. For instance, Kolobow and colleagues found that several hours were necessary to produce lung injury in sheep, even when very high airway pressures were used (24). All the sheep had decreased pulmonary compliance and reduced blood oxygenation after 2 d of mechanical ventilation with 50 cm H_2O peak pressure. Some sheep died before the 48-h endpoint. Pathologic examination of their lungs showed congestion and severe atelectasis. The cause of the lung alterations after long-term ventilation in large animals is probably more composite than that responsible for the rapid onset of edema in smaller ones. This issue is discussed in the section, MECHANISMS OF ALTERED PERMEABILITY. Attention was recently drawn to the fact that mechanical ventilation, even at low airway pressure and tidal volume (VT), may cause additional damage to injured lungs (28–31). We now understand something of the way these injuries develop, although there are still many blanks to fill in.

VENTILATION-INDUCED PULMONARY EDEMA: HYDROSTATIC OR PERMEABILITY EDEMA?

This issue has been a matter of debate for some time, and the answer to this question is not only of theoretical importance. Because the properties of the alveolar–capillary barrier are abnormal during acute lung injury such as the adult respiratory distress syndrome (ARDS), it is essential to ascertain whether mechanical ventilation–induced alterations will only result in further fluid accumulation, or whether they will create new lesions, or aggravate existing ones. In their fundamental contribution to the description of ventilation-induced pulmonary edema, Webb and Tierney (22) speculated that hydrostatic mechanisms were responsible for edema. However, light microscope examination revealed deep eosinophilic staining of interstitial edema fluid, suggesting that this fluid was rich in proteins. The hydrostatic or permeability origin of the edema has subsequently been investigated by several groups. The present state of knowledge suggests that alterations in microvascular permeability are the main determinants of this pulmonary edema.

Experimental Evidence for Increased Vascular Transmural Pressure

The first explanation advanced for ventilation-induced edema was an increase in vascular transmural pressure at both extraalveolar and alveolar levels (22) via mechanisms that will be considered in detail in the section, MECHANISMS OF INCREASED VASCULAR TRANSMURAL PRESSURE.

Few data are available on vascular pressures during high-pressure mechanical ventilation (25, 27). It is difficult to deduce from the reported mean pressures what actually happens at the microvascular level, because of the regional (zone I–IV) inhomogeneity of pulmonary blood flow in the large animals in which these measurements were obtained (32). Moreover, intraregional heterogeneity further complicates this issue, because alveolar corner vessels remain open and may expand during zone I conditions (33–36). Finally, the site of maximum resistance may move as lung volume varies (37). Demonstration of a substantial increase in mean transmural vascular pressure would argue in favor of a hydrostatic origin. No such increase was reported in the literature summarized below.

Parker and colleagues (25) ventilated open-chest dogs for 30 min at 64 cm H_2O peak airway pressure, which resulted in a mild pulmonary edema. They calculated the capillary filtration pressure from measurements of mean pulmonary artery and left atrial pressures. They found that mean microvascular pressure increased by 12.5 cm H_2O. The authors acknowledged that this change in microvascular pressure would probably be even smaller in intact animals because of the decreased cardiac output caused by the high intrathoracic pressure. The better pulmonary hemodynamics in open-chest animals may explain in part the observation by Woo and Hedley-Whyte (38). They reported development of severe lung injury, with pulmonary edema and tracheal flooding, in open-chest dogs after 8 h of ventilation with very large (50 ml/kg body weight [BW]) tidal volumes. By contrast, closed-chest animals ventilated with the same settings showed no discernible abnormality.

The small magnitude of the change in mean transmural microvascular pressure during high airway pressure ventilation was also suggested by the work by Carlton and colleagues (27). They ventilated closed-chest lambs with 58 cm H_2O peak inspiratory pressure and observed that the mean pulmonary arterial pressure increased by 11 cm H_2O and the left atrial pressure by 5 cm H_2O over the baseline values for animals ventilated with 19 cm H_2O peak airway pressure. The resulting change in capillary pressure was therefore mild. In addition, mean intrathoracic (pleural) pressure (referenced to the atmosphere) increased by 4 cm H_2O at the same time, suggesting a rather limited increase in mean transmural microvascular pressure.

The conclusion that can be drawn from these few observations is that there is probably no large, uniform increase in transmural pressure over the whole pulmonary vascular network during high airway pressure ventilation. Either increased filtration by this mechanism is very localized or other mechanisms are involved, especially if one considers the extreme severity of the edema that may be produced in small species, such as rats (4, 5, 22). However, it should be pointed out that theoretical considerations based on lung interdependence predict that considerable increases in regional microvascular transmural pressure may occur during the inflation of very heterogeneous lungs (39). The magnitude of this increase would be such that edema might be not only of the hydrostatic type, but also associated with permeability alterations because of the stretched pore phenomenon (40, 41) or capillary stress failure (42). This point is examined thoroughly in the section on the mechanisms of alterations in permeability.

Evidence for Alterations in Alveolar–Capillary Permeability

By contrast with the lack of firm demonstration that hydrostatic pressure changes are sufficient to cause ventilator-induced edema, major alterations in pulmonary epithelial and, more surprisingly, endothelial permeability have been reported for isolated lungs, as well as for open-chest and intact animals subjected to high airway pressures.

Alterations of alveolar–airway epithelial permeability.

Small solutes. The increase in epithelial permeability to small hydrophilic solutes that occurs as lung volume increases is a physiologic phenomenon. The clearance of aerosolized ^{99m}Tc-DTPA increased when the functional residual capacity (FRC) was increased by positive end-expiratory pressure (PEEP) during mechanical ventilation (43), or spontaneous ventilation (44) in sheep. The changes in clearance were larger than would be expected from those of the alveolar exchange surface area. The same observation has been made in humans (45, 46). An increase in DTPA clearance was obtained regardless of whether the lung volume was changed by positive pressure breathing or voluntary hyperinflation (45). DTPA clearance in intact rabbits increased more after pressure-controlled inverse ratio ventilation than after volume-controlled ventilation with the same end-expiratory pressure (5 cm H_2O) and a normal V_T (47). Prolonged inspiration resulted in a larger time-adjusted lung volume, which could explain the greater increase in epithelial permeability.

Larger solutes: the effects of static inflation of fluid-filled lungs. The equivalent pore approach was used by Egan (48) to describe the permeability of the epithelium to hydrophilic solutes of various sizes during the static overinflation of lobes filled with fluid in closed-chest sheep. The equivalent pore radius of the epithelium increased from about 1 nm at 20 cm H_2O inflating pressure to 5 nm at 40 cm H_2O inflating pressure (Figure 1), reflecting a moderate increase in permeability. But albumin sometimes freely diffused across the epithelium, indicating the presence of large leaks (Figure 1). These findings were subsequently reproduced in dogs (49). The changes in permeability persisted, or even increased after cessation of inflation, suggesting irreversible epithelial injury. However, high airway pressures applied to lobes rather than to the whole lung produced an inflation greatly exceeding the maximal regional capacity. Indeed, hyperinflation limited to a small area of the lung allowed this area to compress other lobes and the contralateral lung, producing an expansion many times greater than what would have been reached if the whole lung were subjected to the same distending pressure. Egan (50) therefore performed experiments in closed-chest rabbits in which both segments and entire lungs were distended with 40 cm H_2O airway pressure for 20 min. Static segmental inflation resulted in 6- to 12-fold increases in volume from FRC and in an epithelium that was permeable to all (small and large) the solutes tested (cyanocobalamin, cytochrome c, and albumin: molecular radius of 0.6, 1.7, and 3.5 nm, respectively). In contrast, inflation of whole lungs resulted in only a 3- to 4-fold increase in lung volume, a much smaller increase in permeability to the smallest solutes, and little or no change in permeability to albumin. Similarly, Kim and Crandall (51) found that the permeability of the epithelium of isolated bullfrog lungs was not modified when inflation remained within the physiologic range, but was increased by overinflation. Hence, only major increases in lung volume alter epithelial permeability to large molecules during static inflation.

Larger solutes: the effects of mechanical ventilation with high airway pressure in intact animals. In contrast to the modest effect of static lung inflation on epithelial permeability, prolonged cyclic lung inflation during mechanical ventilation

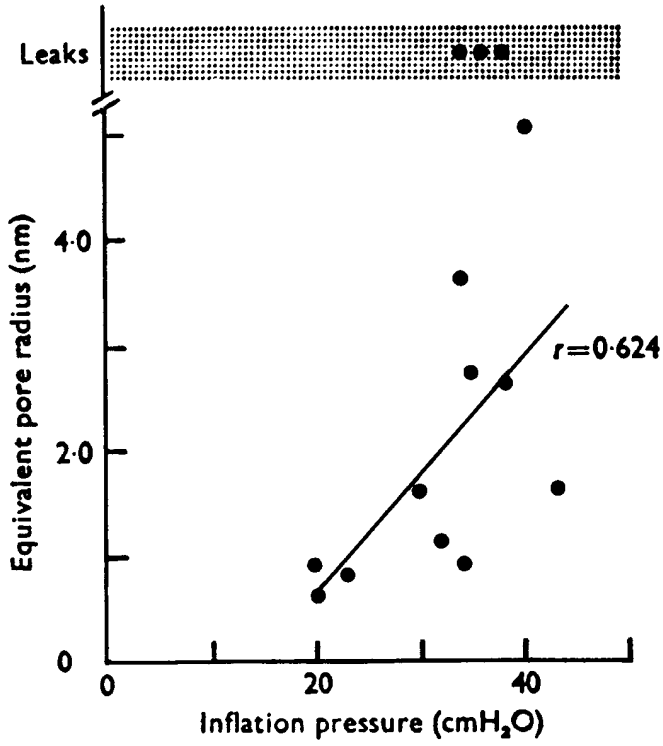

Figure 1. Effect of static inflation on alveolar epithelial permeability (equivalent pore radius) of fluid-filled sheep lobes *in situ*. There was a correlation between inflation pressure and permeability. Albumin diffused freely at the highest pressure, indicating large leaks. Reproduced from Egan and coworkers (48), with permission.

produces severe alterations. Epithelial permeability to large solutes is probably not significantly altered during the early stages of ventilator-induced lung edema provided there is no alveolar flooding. For instance, positive pressure ventilation in lambs with a peak inspiratory pressure of 41 cm H_2O for 8 h did not induce pulmonary edema, but resulted in altered alveolar permeability to small (DTPA) but not large (albumin) solutes (52). Similarly, no obvious increase in alveolar permeability to proteins was observed during the mild pulmonary edema produced by very short periods (several minutes) of high-pressure ventilation in rats (6). But there were undoubtedly major alterations of epithelial permeability later, when pulmonary edema was severe. Indeed, ultrastructural examination revealed widespread destruction of the alveolar epithelium at this stage, which must necessarily alter its barrier properties (4, 5). These abnormalities are detailed under ELECTRON MICROSCOPE STUDIES.

Changes in microvascular permeability during mechanical ventilation at high airway pressures.

Isolated lungs. Parker and colleagues (53) showed that the ventilation of isolated blood-perfused dog lobes for 20 min with graded increases in peak airway pressure up to 30 cm H_2O did not affect microvascular permeability, as assessed by the capillary filtration coefficient (Figure 2). Higher peak inspiratory pressures (45 to 65 cm H_2O, which corresponds to a lung volume well above the total lung capacity in these isolated lungs) increased the capillary filtration coefficient and decreased the isogravimetric capillary pressure (the maximal hydrostatic pressure at which lungs do not gain weight). The estimated protein reflection coefficient was also decreased only at the highest airway pressures. The increase in capillary filtration coefficient observed by Parker and coworkers (53) was immediate when airway pressures were above the 30 cm H_2O threshold, and it sometimes persisted after airway pressure was lowered. These results show that increasing lung volume ultimately alters endothelial permeability to solutes of both small and large molecular weight and suggest the presence of an airway pressure threshold below which these modifications do not occur. However, the fact that edema probably due to increased permeability occurred with a peak inspiratory pressure as low as 13 cm H_2O in isolated perfused rat lungs (54) raises questions about the precise level of such a pressure threshold. This issue will be discussed under POSSIBLE PRESSURE–VOLUME THRESHOLD FOR EDEMA AND PERMEABILITY ALTERATIONS.

Intact animals. Demonstration of microvascular permeability abnormalities was easier in small than in large animals during mechanical ventilation with high airway pressure. The possibility of changes in capillary permeability in intact animals was assessed by measuring extravascular lung water and bloodless dry lung weight in mechanically ventilated rats (4). Dry lung weight increases during edema due to increased permeability, but not during hydrostatic edema (55). Changes in dry lung weight reflect the efflux from the vascular spaces and the accumulation in the interstitium and alveoli of plasma proteins. Changes in permeability were more refinely assessed using the pulmonary extravascular distribution space of intravenously injected ^{125}I-labeled albumin, which reflects the rate at which albumin leaks from blood vessels into the lung. Pulmonary edema developed very rapidly in animals ventilated at 45 cm H_2O peak airway pressure and was readily apparent after only 5 min of ventilation (Figure 3). Light microscope examination revealed a mild edema confined to interstitial spaces, resulting in peribronchovascular cuffs (*detailed in* PATHOLOGIC FINDINGS). No alveolar flooding was apparent at this stage. The presence of unequivocal microvascular permeability alterations was evidenced by significant increases in dry lung

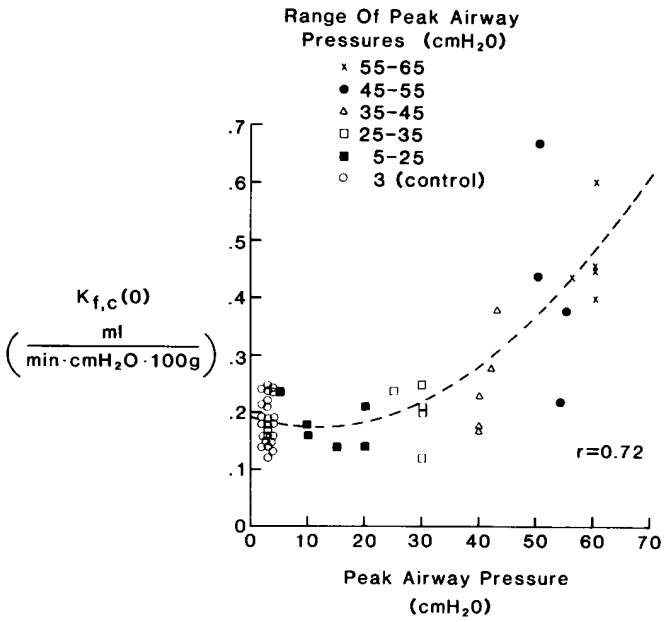

Figure 2. Changes in the capillary filtration coefficient (K_{fc}) of isolated blood-perfused lobes of dog lungs given 20 min of intermittent positive pressure ventilation. Moderate (up to 30 cm H_2O) increases in peak airway pressure did not affect K_{fc}, whereas higher peak pressure produced a steep increase in K_{fc}. Reproduced from Parker and coworkers (53), with permission.

weight and albumin space (Figure 3). Pulmonary edema was more abundant after 10 min of high peak airway pressure ventilation, but still involved only the interstitial spaces. But the findings were strikingly different after 20 min of ventilation, with widespread alveolar flooding in all animals. The severity of the permeability changes was attested by the ^{125}I-albumin activity in the tracheal fluid which was close to that in plasma. Indeed, a high protein concentration in edema fluid strongly suggests permeability type edema (3, 55–58). There were massive increases in extravascular lung water, dry lung weight, and albumin distribution space (Figure 3). The relationship between dry lung weight and extravascular lung water (Figure 4) indicated that the extravasated fluid had the same protein content as plasma, confirming the very severe permeability defect (55) and suggesting the presence of numerous, large capillary leaks. Subsequent studies in closed-chest and open-chest animals using different approaches confirmed that high airway pressure ventilation is associated with changes in microvascular permeability (25, 27, 59). Hernandez and colleagues (59) ventilated closed-chest rabbits with a peak pressure of 45 cm H_2O for 1 h, then removed the lungs and measured the capillary filtration coefficient. It was 430% that of controls ventilated with a peak pressure of 15 cm H_2O. In their work on the contribution of increased filtration to high peak airway pressure edema in open-chest dogs, Parker and coworkers (25) found changes in lymph protein clearance and lymph/plasma protein ratio compatible with altered microvascular protein permeability. Protein clearance and ratio were rather variable, but were significantly higher in dogs that had been ventilated for 30 min with 64 cm H_2O peak airway pressure than in those ventilated for the same time with 22 cm H_2O peak airway pressure. This study did not include a control group, but the lymph–plasma protein ratios in the 22 cm H_2O peak pressure group were comparable to those reported for uninjured lungs

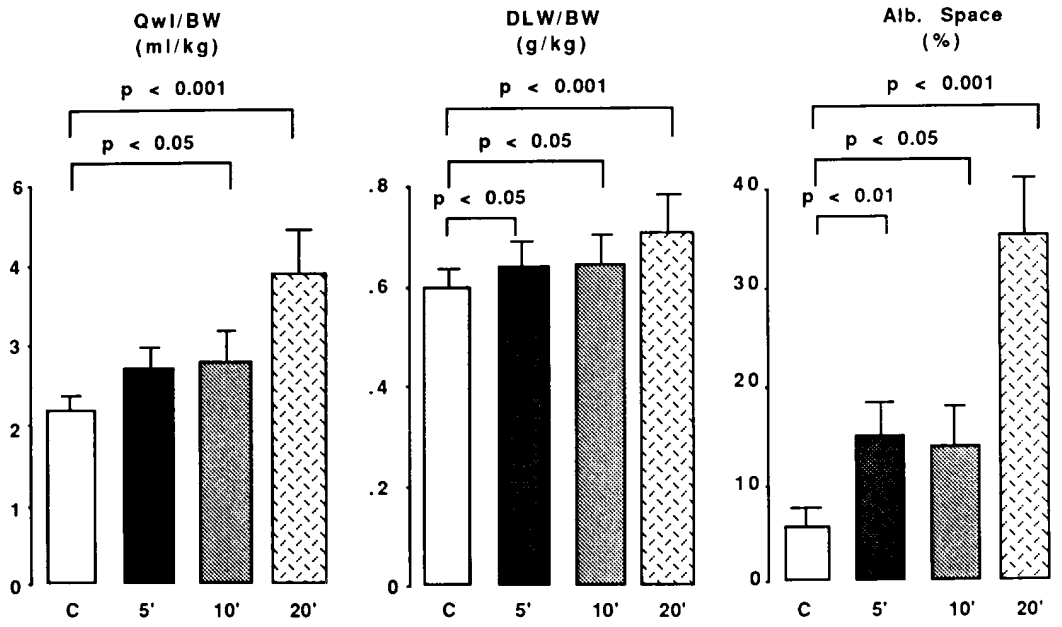

Figure 3. Effect of ventilation at a peak airway pressure of 45 cm H_2O for 5 to 20 min in closed-chest rats. Pulmonary edema was assessed by measuring the extravascular lung water content (Qwl/BW) and changes in permeability by determining the bloodless dry lung weight (DLW/BW), and the distribution space of ^{125}I-labeled albumin (Alb. Space) in lungs. Control rats (C) were ventilated at a peak airway pressure of 7 cm H_2O. Pulmonary edema developed rapidly (5 min) and was associated with changes in permeability. All the indices increased markedly after 20 min of mechanical ventilation ($p < 0.01$ versus other groups). Adapted from Dreyfuss and coworkers (4), with permission.

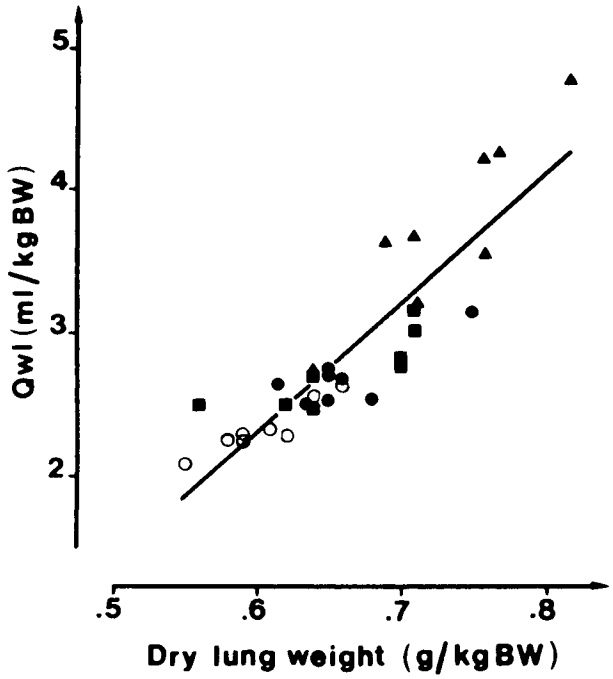

Figure 4. Relationship between extravascular lung water content (Qwl) and dry lung weight during mechanical ventilation with a peak airway pressure of 45 cm H_2O in rats. This relationship was consistent with an edema fluid of high protein content, reflecting severe changes in permeability. *Open circles*: control conditions; *closed circles*: 5 min of ventilation; *closed squares*: 10 min of ventilation; *closed triangles*: 20 min of ventilation. Reproduced from Dreyfuss and coworkers (4), with permission.

(60). The reflection coefficient for total proteins (derived from the slope of lymph protein clearance versus lymph flow) after high (64 cm H_2O) peak pressure ventilation was as low (0.42) as that previously found by these authors (61) in lungs with permeability edema after exposure to the toxin alpha-naphthylthiourea (0.38), suggesting that high peak pressure ventilation may be as deleterious as usual models of toxic lung injury. The variability in the permeability changes may have been due to the study design, which consisted of rather short periods of high-pressure ventilation (30 min only) in large animals (dogs). The amount of edema was mild in these dogs under such conditions, probably because it takes more time for overinflation edema to occur in large animals than in small ones. This may have precluded accurate assessment of permeability changes. These changes may become detectable only after longer ventilation times, in contrast to the immediate occurrence of microvascular pressure changes. Another potential factor which may have led to underestimation of the permeability alterations in the study by Parker and colleagues (25) is that 1 h elapsed between the ventilation challenge and measurement of the reflection coefficient. Microvascular permeability has been shown to rapidly return to normal after short periods of high-pressure ventilation (6) (*see* REVERSIBILITY OF LIMITED ABNORMALITIES).

Increased microvascular permeability was also reported by Carlton and colleagues in lambs mechanically ventilated with 61 cm H_2O peak airway pressure. There was a very important (3- to 13-fold) increase in lung lymph flow. The presence of permeability alterations was ascertained by the unchanged lymph–plasma protein concentration ratio during edema development (27).

Whatever their respective magnitude, increased microvascular filtration pressure and altered microvascular permeabil-

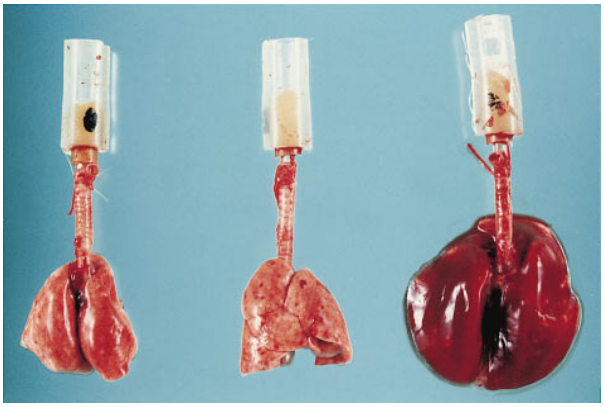

Figure 5. Macroscopic aspect of rat lungs after mechanical ventilation at 45 cm H_2O peak airway pressure. *Left*: normal lungs; *middle*: after 5 min of high airway pressure mechanical ventilation. Note the focal zones of atelectasis (in particular at the left lung apex); *right*: after 20 min, the lungs were markedly enlarged and congestive; edema fluid fills the tracheal cannula.

ity probably act in concert to produce high airway pressure pulmonary edema. Even if the hydrostatic component is probably moderate, at least in closed-chest animals, it may have important consequences. Any increase in driving pressure will favor edema when the sieving properties of the microvascular barrier are abnormal (62–64). The synergistic actions of hydrostatic forces and altered permeability may explain the (occasional) occurrence of fulminating pulmonary edema.

Pathologic findings. Animal lungs injured by mechanical ventilation display a pattern of atelectasis, severe congestion and enlargement because of edema (22, 24, 26). There is an obvious relationship between the duration of the injury and the overall appearance of the lung (Figure 5). Figures 5 through 8 show the changes revealed by gross pathologic, light microscopic, and electron microscopic examinations during VILI of different severity in rats. Ventilator-induced pulmonary edema is associated with severe endothelial and epithelial abnormalities, the structural counterpart of the alterations in permeability (4–6).

Light microscope studies. Interstitial and alveolar edema have been reported after mechanical ventilation with high peak airway pressure (4, 22, 23). The degree of edema varies with the magnitude of the peak airway pressure (22) and the duration of mechanical ventilation (4). Edema is initially confined to the interstitial spaces and is visualized as peribronchovascular cuffs (56, 65) under the light microscope (Figure 6A). High peak pressure mechanical ventilation for less than 1 h causes profuse alveolar edema (Figure 6B). Although it is difficult to assess the respective responsibility of hydrostatic and permeability alterations on the basis of light microscopic examination alone, certain histologic features suggest that permeability changes are prominent in ventilation-induced pulmonary edema. As already mentioned, Webb and Tierney (22) found that the edema in their moribund animals was deeply eosinophilic, suggesting that it was rich in proteins and, hence, might be an exsudate rather than a transudate. Changes in permeability during high airway pressure–large tidal volume mechanical ventilation are also suggested by the observations reported by Tsuno and coworkers (66) for baby pigs. The pigs were ventilated with a peak inspiratory pressure of 40 cm H_2O for about 22 h to produce overinflation lung injury characterized by severe hypoxemia. Some were killed immediately after this period of high-pressure ventilation, whereas the others were subsequently supported with normal pressure and volume mechanical ventilation for several days. Microscopic examination of the lungs of animals killed immediately after the high-pressure ventilation period showed severe diffuse alveolar damage, with hyaline membranes, alveolar hemorrhage, and neutrophil infiltration. These alterations were similar to those found during the early stages of human ARDS. The piglets kept for several days after being injured by high-volume ventilation also had damaged lungs that looked similar to lungs in late stage ARDS, with collapsed alveolar spaces and proliferation of fibroblasts and type II cells.

The difference between the pathologic appearance of the lungs of small animals (4, 5, 22) and those of larger ones (66) at the early stage of VILI is probably related to the differing durations of the challenge. Edema develops so rapidly (a few minutes) in small animals that there is not enough time for the development of noticeable inflammation and neutrophil infiltration of lung tissue. In contrast, the several hours necessary to produce patent edema in larger animals is sufficient for

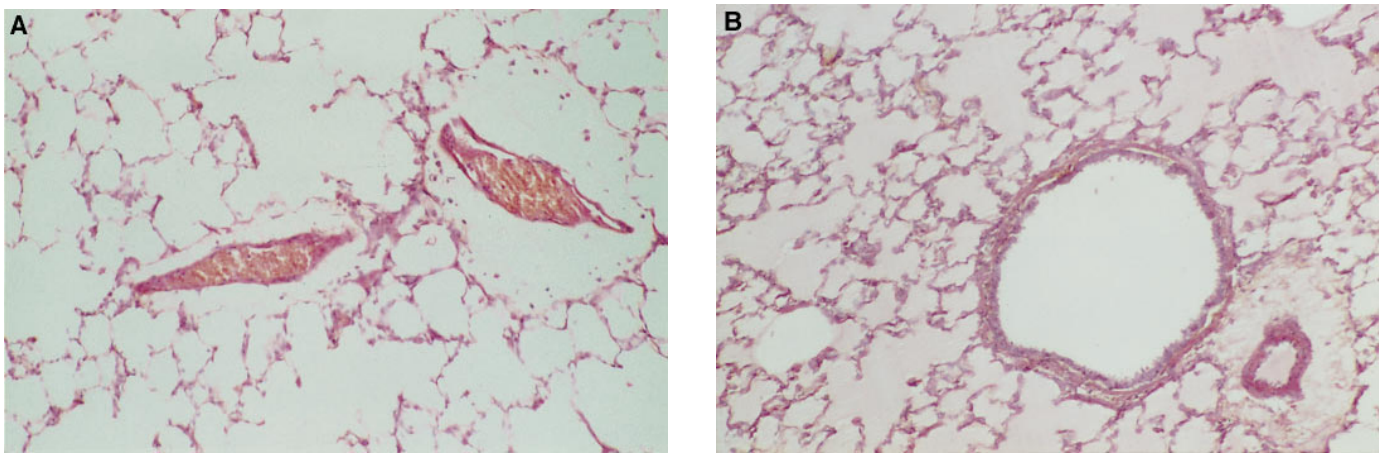

Figure 6. Light microscope appearance of rat lungs after mechanical ventilation at 45 cm H_2O peak airway pressure. (*A*) After 5 min of ventilation, interstitial edema is found in large perivascular cuffs. (*B*) After 20 min of ventilation, there is widespread alveolar edema that fills nearly all the alveoli on this slide. These figures were kindly provided by Dr. Paul Soler.

activation, adherence, and significant migration of neutrophils into airspaces (66, 67). The importance of this distinction will be highlighted in the section devoted to the mechanisms of VILI.

Electron microscope studies. Electron microscope observations clearly showed the major abnormalities that resulted in increased permeability during VILI. Discontinuities in alveolar type I cells have been reported in rabbits ventilated with moderate (20 cm H_2O) peak airway pressure for 6 h (68). Widespread alterations of endothelial and epithelial barriers were evidenced when a higher peak airway pressure was used (4–6). If VILI were the result of changes in hydrostatic forces only, there should be no (7, 8, 69) or little (70, 71) ultrastructural alteration.

As detailed above, the lungs of rats ventilated for short periods (5 to 10 min) with 45 cm H_2O peak airway pressure had only interstitial edema by light microscopic examination (Figure 6A). In addition to the confirmation of interstitial edema, electron microscopy revealed endothelial abnormalities (Figure 7) similar to those found during toxic pulmonary edema, showing that the ventilation edema was of the nonhydrostatic type (4). Some endothelial cells were detached from their basement membrane, resulting in the formation of intracapillary blebs that were filled with a material having the same density as plasma (Figure 7a). There were also occasional breaks in endothelial cells (Figure 7b). Ventilation for longer periods resulted in alveolar flooding (Figure 6B) and diffuse alveolar damage (Figure 8) (4). There were profound alterations in the epithelial layer in addition to the capillary lesions. The severity of the alterations was unevenly distributed: the epithelial lining appeared to be intact in some areas, whereas there were discontinuities and sometimes almost complete destruction of type I cells in many others, leaving a denuded basement membrane (Figure 8). In contrast, type II cells always appeared to be preserved. Hyaline membranes filled the alveolar spaces in most of the sections examined of animals with severe alveolar edema (4, 5) (Figure 8). Endothelial breaks allowed direct contact between polymorphonuclear neutrophils and the basement membrane (Figure 8). The severity of alveolar cell destructions probably explains the marked elevation of lung lavage cellular enzymes such as lactate dehydrogenase and aspartate aminotransferase observed in rats with VILI (72). Interestingly, alveolar edema and epithelial destructions were prevented by the application of a 10 cm H_2O PEEP (Figure 9) (5). This point will be discussed in the following section.

These electron microscopy findings strongly support the contention that permeability alterations are a main determinant of ventilator-induced pulmonary edema. Indeed, endothelial blebs like those shown in Figure 7 have been reported only in experimental high-permeability edema, regardless of the causative agent, and in ARDS (7–10). Ultrastructural studies of experimental hydrostatic pulmonary edema in intact animals have disclosed no such alterations (7, 8, 69). Hydrostatic type edema was for a long time not considered to be associated with ultrastructural cellular abnormality, at either the microvascular or epithelial levels (7, 69, 73). It is only very recently that refined ultrastructural studies have shown epithelial breaks and blebbing and rare endothelial lesions in excised rabbit lungs with vascular pressures in the 30 mm Hg range (70, 71). These mild changes are quite different from those observed recently when transmural capillary pressure is raised very high (more than 50 mm Hg) in isolated lungs, leading to the very particular entity termed "capillary stress failure". This entity will be discussed in the section devoted to the mechanisms of ventilator-induced lung injury.

CONTRIBUTIONS OF THE STATIC AND DYNAMIC LUNG VOLUME COMPONENTS TO VENTILATOR-INDUCED EDEMA

High-volume ventilation may overstretch both normal and diseased alveoli and thus directly produce lung injury. Re-

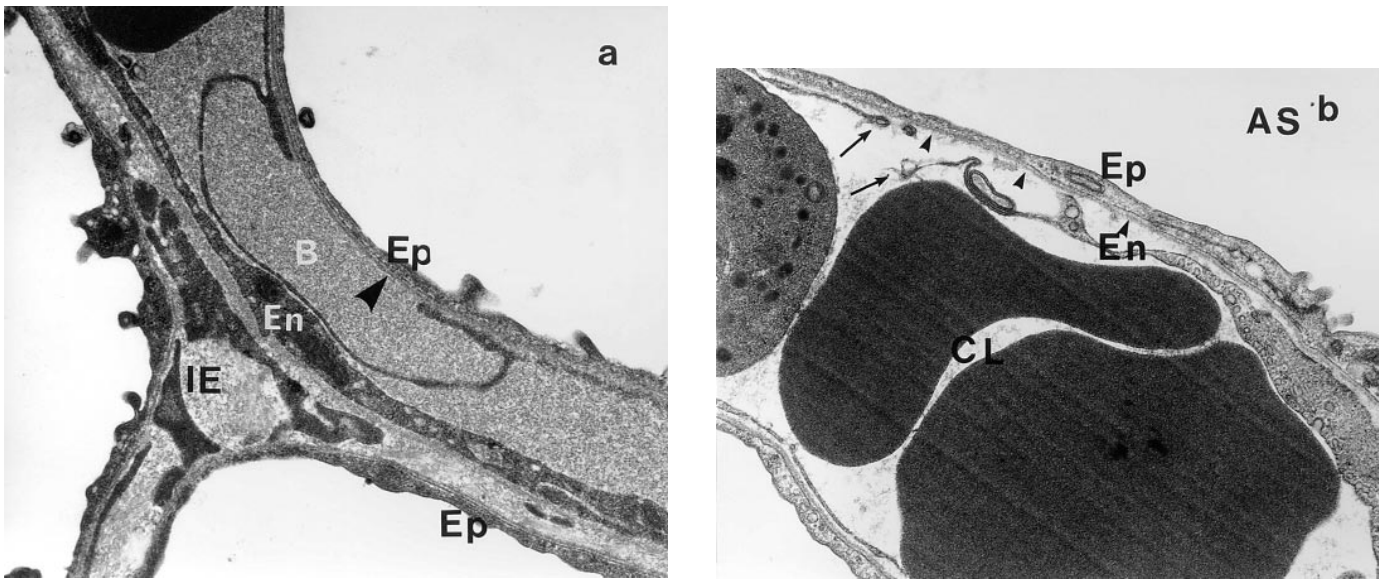

Figure 7. Early changes (5 min) in the ultrastructural appearance of the blood–air barrier after mechanical ventilation of a closed-chest rat at 45 cm H_2O peak airway pressure. (*a*) The thin part of an endothelial cell (En) is detached from the basement membrane (*arrowhead*) forming a bleb (B) filled with electron-dense material of the same density as the plasma. Epithelial type I cells (Ep) are intact. Note interstitial edema (IE). (*b*) The thin part of the endothelial cell is disrupted and floats in the capillary lumen (*arrows*) after becoming detached from the basement membrane (*arrowheads*). AS = alveolar space. *Panel a* was kindly provided by Dr. Paul Soler. *Panel b* is reproduced from D. Dreyfuss and G. Saumon. Ventilator-induced lung injury. *In* M. J. Tobin, editor. Principles and Practice of Mechanical Ventilation. McGraw-Hill, New York. 793–811, with permission.

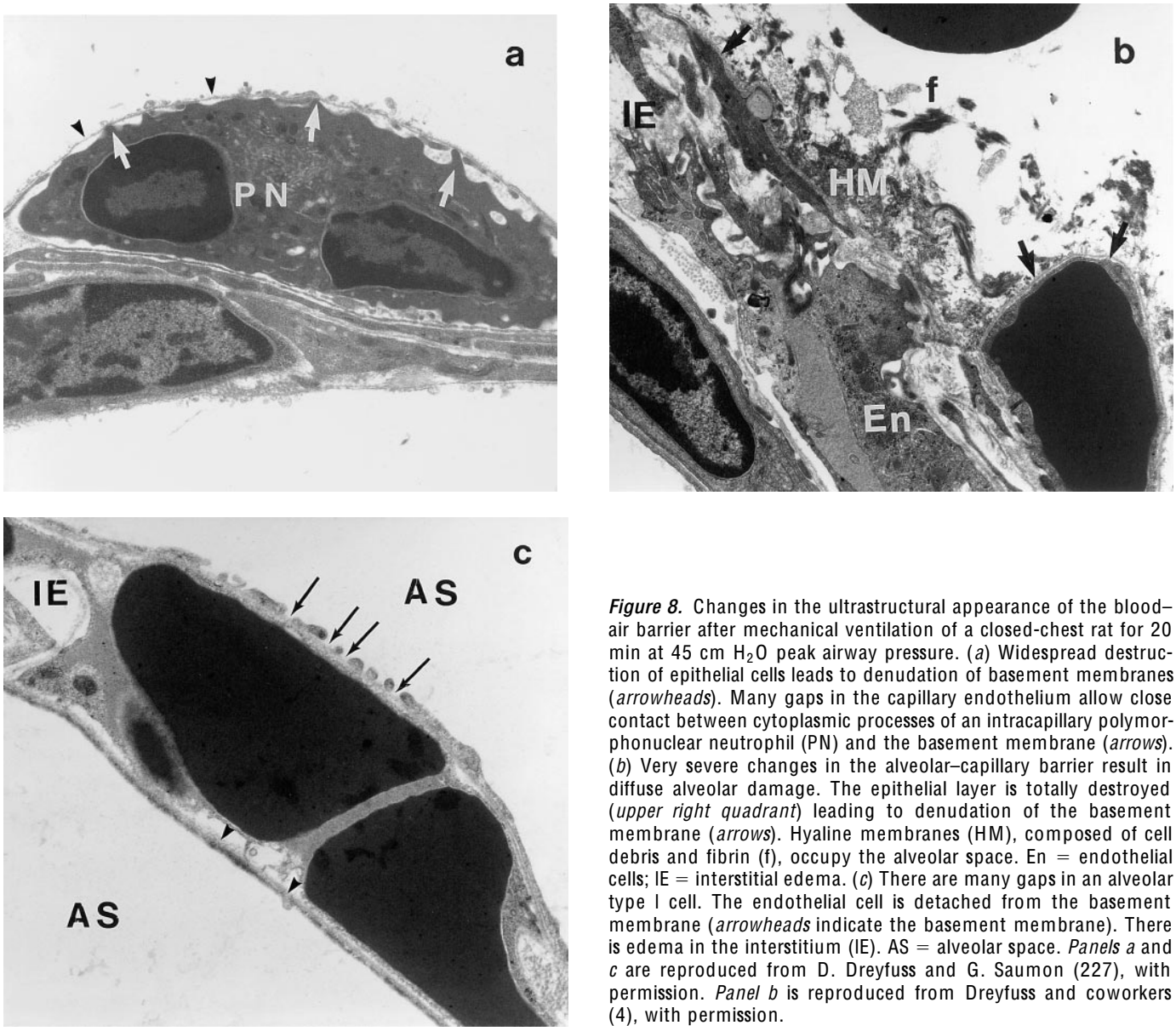

Figure 8. Changes in the ultrastructural appearance of the blood–air barrier after mechanical ventilation of a closed-chest rat for 20 min at 45 cm H_2O peak airway pressure. (*a*) Widespread destruction of epithelial cells leads to denudation of basement membranes (*arrowheads*). Many gaps in the capillary endothelium allow close contact between cytoplasmic processes of an intracapillary polymorphonuclear neutrophil (PN) and the basement membrane (*arrows*). (*b*) Very severe changes in the alveolar–capillary barrier result in diffuse alveolar damage. The epithelial layer is totally destroyed (*upper right quadrant*) leading to denudation of the basement membrane (*arrows*). Hyaline membranes (HM), composed of cell debris and fibrin (f), occupy the alveolar space. En = endothelial cells; IE = interstitial edema. (*c*) There are many gaps in an alveolar type I cell. The endothelial cell is detached from the basement membrane (*arrowheads* indicate the basement membrane). There is edema in the interstitium (IE). AS = alveolar space. *Panels a* and *c* are reproduced from D. Dreyfuss and G. Saumon (227), with permission. *Panel b* is reproduced from Dreyfuss and coworkers (4), with permission.

cently, attention has focused on the potential for ventilation at low lung volume (i.e., with a reduced FRC) to worsen preexisting lesions, through the periodic opening and closing of distal airspaces. The specific effect of ventilation on diseased lungs will be discussed in the section, Effects of High-volume Ventilation on Abnormal Lungs.

High-volume Lung Edema

Roles of increased airway pressure and increased lung volume. The high intrathoracic pressures that occur during mechanical ventilation result in large lung volumes, provided the respiratory system is sufficiently compliant. However, these high pressures also have hemodynamic effects in the systemic circulation (74) and in the lungs, where blood flow distribution may be affected by the extension of zone 1 conditions during overinflation. Several studies have examined the roles of intrathoracic pressure and lung distention in the genesis of pulmonary edema.

Experimental studies often indicate the peak airway pressure reached during mechanical ventilation. Given the fact that ventilator-induced injury depends mainly on lung volume, and in particular the end-inspiratory volume, it would be more appropriate to indicate the end-inspiratory (plateau) pressure. The clinical importance of plateau pressure was recently underlined in a Consensus Conference on mechanical ventilation (12). In the experiments in rats reported below, the increase in inspiratory pressure was monotonic, with the end of inspiration being under quasi-static condition, so that the maximal airway pressure coincided with end-inspiratory volume.

Intact rats were subjected to large or low V_T ventilation, but with identical peak airway pressures (45 cm H_2O) to distinguish between the effects of lung distention and increased intrathoracic pressure (5). Low-volume ventilation with high airway pressure was obtained by limiting thoracoabdominal excursions by strapping during conventional, intermittent positive airway pressure ventilation. The rats subjected to high tidal volume–high airway pressure ventilation developed permeability pulmonary edema (Figure 10) with ultrastructural abnormalities as described above (5). In striking contrast, strapped animals ventilated with a high airway pressure but a normal

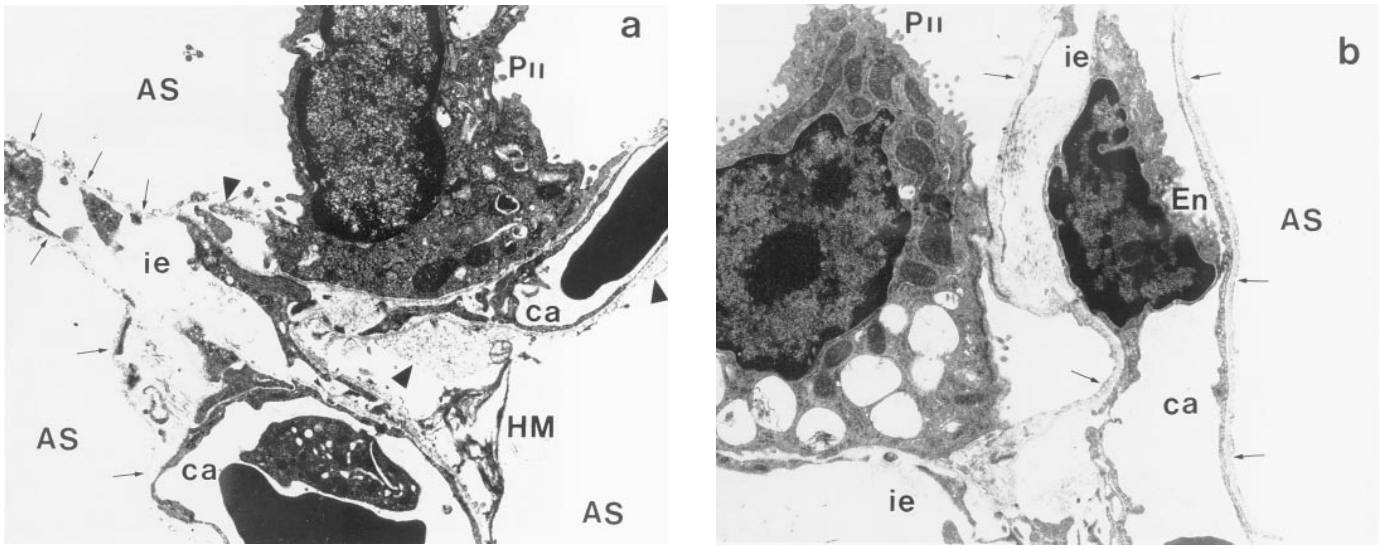

Figure 9. Ultrastructural aspect of the lungs of intact rats mechanically ventilated at 45 cm H_2O peak airway pressure with a 10 cm H_2O PEEP. (*a*) No PEEP: there is diffuse alveolar damage (*see* legend of Figure 8 for details). (*b*) With PEEP: type I cells appear intact (*arrows*). The only abnormalities are interstitial edema (ie) and focal endothelial blebs (not shown). Reproduced from Dreyfuss and coworkers (5), with permission.

VT had no edema (Figure 10) and the ultrastructure of their lungs appeared normal (5). To further demonstrate that high airway pressures are not a prerequisite for pulmonary edema, rats were ventilated with large VT but negative airway pressures by means of an iron lung. Permeability edema developed even when airway pressure was negative (Figure 10) (5). The conclusion of this study was that the increase in VT is responsible for ventilator-induced pulmonary edema and not high airway pressure per se. It would therefore be wise to replace the term barotrauma by "volutrauma" (6, 75).

These findings have been replicated in several species, using different approaches. Hernandez and associates (59) studied the effects of ventilation at three peak airway pressures (15, 30, and 45 cm H_2O) and that of ventilation with the same

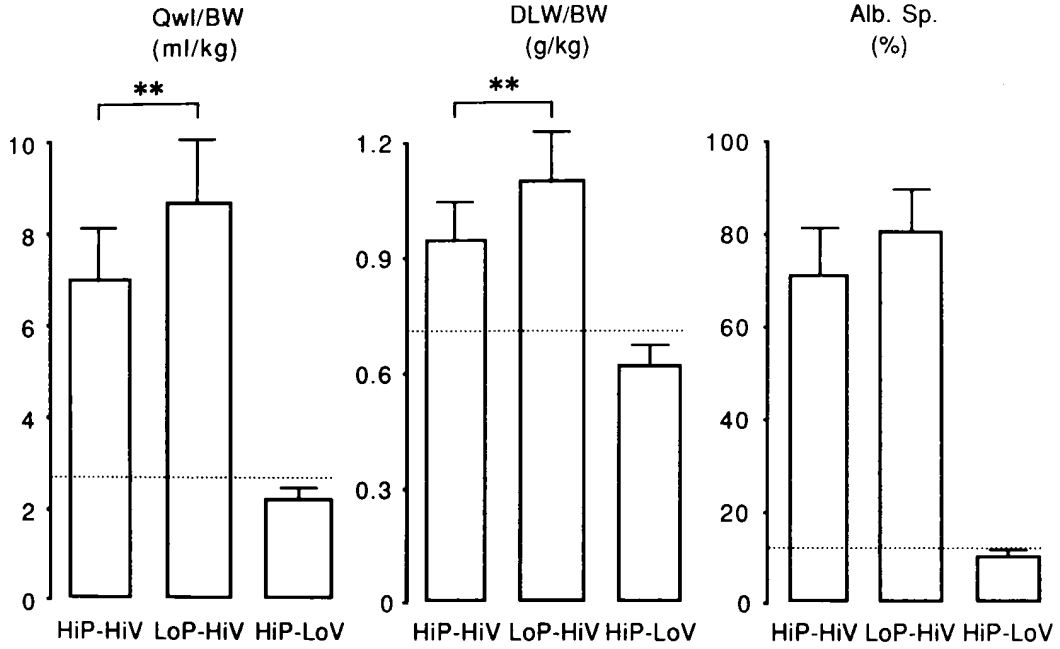

Figure 10. Comparisons of the effects of high-pressure–high-volume ventilation (HiP–HiV) with those of negative inspiratory airway pressure high tidal volume ventilation (iron lung ventilation = LoP–HiV) and of high-pressure–low-volume ventilation (thoracoabdominal strapping = HiP–LoV). *Dotted lines* represent the upper 95% confidence limit for control values. *See* Figure 3 for details on edema indices. Permeability edema occurred in both groups receiving high VT ventilation. Animals ventilated with a high peak pressure and a normal VT had no edema. Reproduced from Dreyfuss and coworkers (5), with permission.

peak pressures but with thoracic excursion restricted by placing plaster casts around the chest and abdomen of rabbits. The capillary filtration coefficient of the lungs removed after ventilation was normal in animals ventilated at 15 cm H_2O peak pressure, increased by 31% after ventilation at 30 cm H_2O peak pressure and by 430% after ventilation at 45 cm H_2O peak pressure in the animals without VT restriction. Restricting lung inflation with the plaster cast prevented this increase in the filtration coefficient, even at the highest peak airway pressure. Carlton and coworkers confirmed this observation in lambs (27). In animals ventilated for 4 to 8 h with a peak inspiratory pressure of 58 cm H_2O, lung lymph flow increased 6-fold in the absence of volume limitation, but remained unchanged when the chest and abdomen were strapped. This pivotal role of lung distention was further emphasized by Adkins and colleagues (76), who observed that the lung capillary filtration coefficient increased more in young rabbits than in adult ones after 30 to 55 cm H_2O peak pressure ventilation, probably because the lung and chest wall compliance of the young animals was larger, allowing greater distention for the same peak airway pressure. Besides the lung distention that occurs during mechanical ventilation, the rate at which lung volume varies may also affect microvascular permeability. Peevy and coworkers (77) determined the capillary filtration coefficient in isolated perfused rabbit lungs ventilated with various tidal volumes and inspiratory flow rates. They found that, for the same peak airway pressure of 53 cm H_2O small tidal volume ventilation (9 to 12 ml/kg BW) with a high flow rate (8.3 L/min) increased the filtration coefficient to the same extent (about 6 times baseline value) as ventilation with a markedly higher VT (25 to 35 ml/kg) but a low inspiratory flow rate (1.9 L/min).

All these studies suggest that, at least in normal lungs, large lung volumes but not high intrathoracic pressures per se are crucial in the genesis of ventilator-induced lung edema. High inspiratory flow rates may aggravate lesions, except that this was shown only in isolated lungs (77). In intact animals, increased intrathoracic pressure produces specific hemodynamic alterations which may conceal the role played by other factors, as discussed in the next section.

Roles of VT, PEEP, and overall lung distention. The consequences of PEEP during acute lung injury or pulmonary edema have sometimes been misinterpreted, mainly because of failure to distinguish between its direct effects, which are to increase FRC and open the lung, and its indirect effects, which are to displace end-inspiratory volume toward total lung capacity when VT is kept constant. Thus, any beneficial effect of PEEP may be offset by the consequences of lung distention. The increase in mean intrathoracic pressure produced by PEEP will also affect hemodynamics (74), and consequently lung fluid balance. The effects of PEEP must therefore be analyzed systematically.

Extensive studies have been done on intact animals and isolated lungs during hydrostatic or permeability type edema to clarify the relationships between PEEP, oxygenation, and the accumulation of extravascular lung water. The effects of PEEP on lung water content seem to depend on whether the study is performed on intact animals or on isolated lobes, on the level of PEEP and its effect on inspiratory airway pressure, and on whether VT is reduced.

Effects of PEEP, with VT kept constant. If the application of PEEP is followed by a significant change in FRC (depending on the shape of the pressure–volume curve), it may result in overinflation of the more distensible areas, depending on the magnitude of VT and the homogeneity of ventilation distribution. Overinflation is probably the explanation for the usual lack of reduction or even the worsening of edema reported with PEEP during most experiments (78).

The differing responses of intact animals and isolated lungs to PEEP is well illustrated by the study by Caldini and colleagues (79). They showed that PEEP as high as 20 mm Hg reduced shunt but did not oppose the formation of hydrostatic edema in closed-chest dogs. A lower PEEP (8 to 10 mm Hg) increased the accumulation of water in isolated lobes perfused at a constant blood flow rate. It seems likely that such a high PEEP (20 mm Hg) applied in closed-chest animals decreased cardiac output. Neither pulmonary blood flow nor lung vascular pressures were measured in the intact animals in this study, thus a reduction in microvascular filtration pressure as compared with isolated lungs may have escaped detection, but would explain this difference in lung fluid balance. Moreover, PEEP probably resulted in greater FRC and end-inspiratory volume for the same VT in isolated lobes than in closed-chest animals, producing some degree of overinflation which may have contributed to its aggravating effect, as discussed subsequently. In fact, PEEP aggravated edema in isolated, ventilated-perfused canine pulmonary lobes injured by the intrabronchial instillation of hydrochloric acid (80). Lobes were ventilated with the same VT and various PEEP levels applied just after acid instillation. Pulmonary blood flow was kept constant. Edema fluid accumulated at the same rate in the presence of a 5 cm H_2O PEEP (which may be considered to allow the maintenance of physiologic residual capacity in isolated lungs) and at 10 cm H_2O PEEP, whereas shunt was significantly lower with this higher PEEP. Shunt was not further reduced by increasing PEEP to 15 cm H_2O but there was twice as much edema (Figure 11) and peak inspiratory pressure was markedly higher with this PEEP. The authors concluded that PEEP had beneficial effects on gas exchange, but worsened

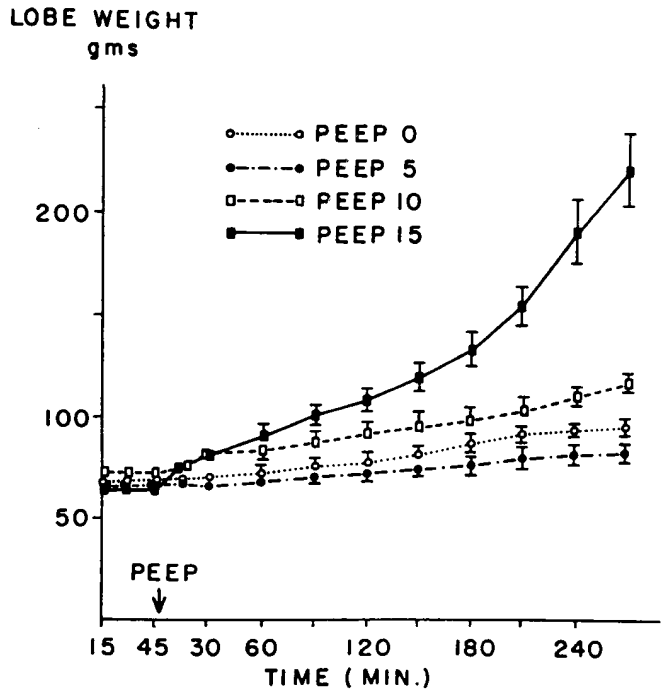

Figure 11. Effect of three levels of PEEP on water accumulation in hydrochloric acid–injured ventilated-perfused dog pulmonary lobes. The highest PEEP resulted in a further increase in pulmonary edema. Reproduced from Toung and coworkers (80), with permission.

pulmonary edema during acute lung injury. The improvement of oxygenation is the consequence of the reopening of flooded alveoli because of the redistribution of edema fluid toward interstitial spaces (35, 81, 82).

Hopewell and Murray also found that a 10 cm H_2O PEEP did not counteract the accumulation of edema fluid during hydrostatic type edema in intact dogs (83). PEEP nevertheless improved oxygenation and mechanical lung properties, as illustrated by the lower peak inflation pressure for a given VT in animals ventilated with PEEP (83). Comparable observations were made during acute lung injury and permeability type edema by Hopewell, who reported that closed-chest dogs whose lungs were injured with alloxan had the same amount of pulmonary edema whether they were on 0 or 10 cm H_2O PEEP when VT was kept constant (84). Peak airway pressure increased in exact proportion to the level of PEEP, and cardiac output was reduced in the animals ventilated with PEEP, suggesting a decrease in microvascular filtration pressure. Similarly, prophylactic application of 10 cm H_2O expiratory positive airway pressure (a form of PEEP) did not reduce edema formation during oleic acid injury in closed-chest dogs (85).

In contrast with the above studies, which all showed no change in the amount of pulmonary edema in intact animals ventilated with PEEP, two teams reported apparently conflicting findings (86, 87). Demling and associates (86) found that PEEP aggravated lung edema in intact animals. They measured the extravascular lung water content in closed-chest dogs in which hydrostatic edema was induced by lobar venous occlusion. Animals ventilated with a 10 cm H_2O PEEP had a significantly higher lobar increase in lung water content than those ventilated with zero end-expiratory pressure, despite comparable net intravascular filtration pressures. However, these animals were ventilated with a large VT (25 ml/kg BW). Such a VT in the presence of PEEP may have increased end-inspiratory volume sufficiently to produce supplemental injury (88, 89). This point will be considered in the following section. The recent study by Colmenero-Ruiz and coworkers (87) investigated the effect of a 10 cm H_2O PEEP on the postmortem extravascular lung water content of pigs ventilated with a normal VT (12 ml/kg BW) after acute lung injury caused by the intravenous infusion of oleic acid. Animals subjected to PEEP had higher mean intrathoracic pressure and significantly less edema than those ventilated with zero end-inspiratory pressure. It is possible that the reduction in edema was caused by the decreased cardiac output (due to higher airway pressure) and filtration in those animals subjected to PEEP. The decrease in cardiac output was important (25%), but did not reach significance perhaps because of a type-2 statistical error caused by the small number of experiments.

These observations show that, for a given VT, increasing FRC with PEEP has different effects on the amount of edema in isolated lungs and in intact animals. The usual lack of effect of PEEP on edema formation in intact animals probably depends on the balance between the PEEP-induced increase in end-inspiratory volume which will favor fluid filtration in extra-alveolar vessels because of lung interdependence (this concept will be detailed in the section, INCREASED TRANSMURAL PRESSURE IN EXTRA-ALVEOLAR VESSELS) and the hemodynamic depression due to elevated intrathoracic pressure which will decrease filtration pressure (*see following section*). The preservation of perfusion in isolated lungs favors the increase in edema.

The situation is different when end-inspiratory volume is controlled by VT reduction during application of PEEP.

Effects of PEEP, with end-inspiratory volume kept constant. All published studies report that ventilation with PEEP and reduced VT is less injurious than ventilation with zero end-expiratory pressure and a higher VT for the same peak airway pressure. Webb and Tierney showed that edema was less severe when a 10 cm H_2O PEEP was applied during ventilation with 45 cm H_2O peak airway pressure (22). This resulted in a lower extravascular lung water content than in animals ventilated without PEEP. They attributed this beneficial effect of PEEP to the preservation of surfactant activity (the importance of surfactant activity in the control of lung fluid balance and the effect of PEEP on surfactant function is discussed in the section on INCREASED TRANSMURAL PRESSURE IN ALVEOLAR VESSELS). It was subsequently shown (5) that PEEP decreased the amount of edema, but did not change the severity of the permeability alterations, as assessed by the increase in dry lung weight, with respect to that in extravascular lung water (5). Edema remained confined to the interstitium in the presence of PEEP, whereas alveolar flooding occurred in its absence (5, 22). As already mentioned, whereas diffuse alveolar damage occurred in animals ventilated without PEEP, no such alteration was observed in the lung epithelium of animals ventilated with PEEP (Figure 9). The only ultrastructural abnormality was endothelial blebbing. The possible explanations for this intriguing observation will be discussed subsequently.

PEEP reduces the VT and increases the mean intrathoracic pressure when end-inspiratory pressure and thus volume are fixed, and each of these can affect edema formation. Studies on perfused canine lobes *in situ* (90) have shown that the rate of hydrostatic edema formation increases with VT for equivalent perfusion flow rates and microvascular pressures. When identical increases in mean airway pressure were produced by applying PEEP or by increasing VT, edema developed less rapidly under PEEP, suggesting that large cyclic changes in lung volume promote edema. This was also the conclusion of the study by Corbridge and coworkers (91), who observed that ventilating dogs with hydrochloric acid–injured lungs with a small VT and a high PEEP produced less edema than ventilation with a large VT and a low PEEP at the same end-inspiratory volume, despite identical cardiac outputs and pulmonary vascular pressures. In keeping with this observation, it was recently shown (87) that ventilation of pigs having oleic acid–induced lung injury with 10 cm H_2O PEEP resulted in less edema when the VT was reduced from a normal (12 ml/kg BW) to a low value (6 ml/kg BW).

For a given end-inspiratory airway pressure, the application of PEEP produces an increase in mean intrathoracic pressure, which adversely affects cardiac output (35, 74). This decrease in cardiac output could explain the abovementioned finding that rats ventilated with 45 cm H_2O peak airway pressure and a 10 cm H_2O PEEP had less edema than those ventilated at the same peak pressure but without PEEP (5, 22). When the fall in systemic arterial pressure consecutive to this ventilation modality was corrected by dopamine infusion, the edema was more severe (Figure 12) (88). The amount of edema was correlated with the systemic blood pressure, suggesting that increased filtration (because of higher pulmonary capillary pressure) was responsible for this aggravation. Nevertheless, the animals ventilated with PEEP that received dopamine had less edema than those with no PEEP, despite similar arterial pressures, suggesting that hemodynamic alterations were not the only explanation for the effect of PEEP on pulmonary edema formation (Figure 12).

In conclusion, the reduction of edema and severity of cell damage by PEEP during ventilation-induced edema may be linked to reduced lung tissue stress (by decreasing VT), and capillary filtration (at least in part because of hemodynamic depression), as well as to the preservation of surfactant, as suggested by Webb and Tierney (22). This latter point will be

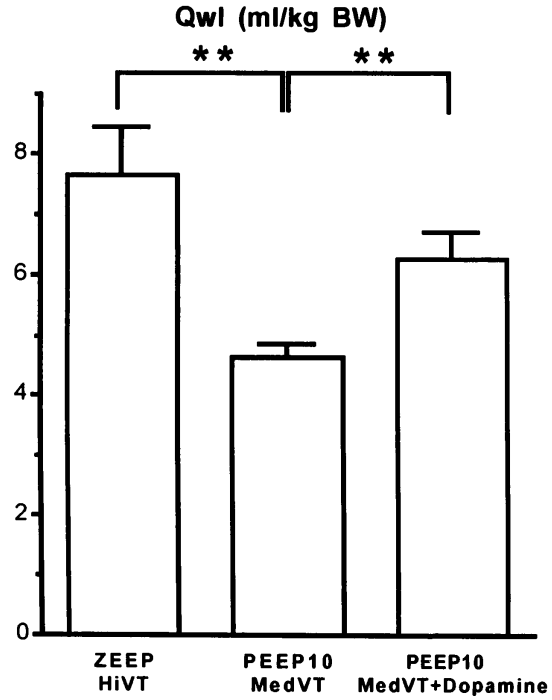

Figure 12. Effect of hemodynamic support with dopamine during 45 cm H_2O peak pressure ventilation with 10 cm H_2O PEEP on the amount of edema as evaluated by extravascular lung water. Compared with animals ventilated with the same peak pressure and ZEEP, those ventilated with PEEP had less edema. This reduction of edema associated with PEEP was partly abolished when dopamine was administered. **$p < 0.01$. Adapted from Dreyfuss and Saumon (88), with permission.

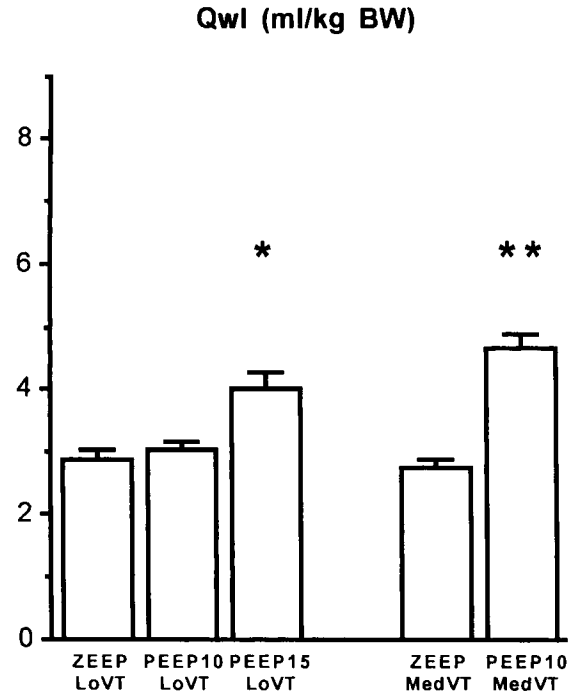

Figure 13. Effect of increasing PEEP from 0 to 15 cm H_2O during ventilation with two different V_T values (7 ml/kg BW: Lo V_T and 14 ml/kg BW: Med V_T). Pulmonary edema (as evaluated by increases in extravascular lung water) occurred when PEEP was increased. The PEEP required to produce edema varied with the V_T: 15 cm H_2O PEEP during ventilation with a low V_T and 10 cm H_2O PEEP during ventilation with a moderately increased V_T. *$p < 0.05$; **$p < 0.01$ versus ZEEP and the same V_T. Reproduced from Dreyfuss and Saumon (88), with permission.

examined in the section on increased transmural pressure in alveolar vessels.

Effects of increasing PEEP when V_T is kept constant: importance of end-inspiratory volume. The overall degree of lung distention, or the end-inspiratory volume, is probably one of the most harmful factors that contributes to the development of ventilator-induced edema. Hence, rats ventilated with a low V_T (7 ml/kg BW) plus 15 cm H_2O PEEP developed pulmonary edema, whereas those rats ventilated with the same V_T plus a 10 cm H_2O PEEP did not (Figure 13) (88). Doubling the V_T, which nevertheless remained within the physiologic range, produced pulmonary edema only in animals ventilated with a 10 cm H_2O PEEP (Figure 13). Thus, even small V_T may be harmful if FRC is sufficiently increased. The important role of uncontrolled increases in end-inspiratory volume in the genesis of VILI when functional residual capacity is increased with PEEP was also illustrated by the work by Muscedere and colleagues (31). Large airway leaks occurred in two of nine surfactant-depleted isolated rabbit lungs ventilated with a low V_T (5 to 6 ml/kg BW) and a PEEP at around 25 cm H_2O (the results of this study will be further detailed in the discussion of low lung volume injury).

In conclusion, mechanical ventilation–induced lung edema may occur whenever there is a certain degree of overall lung overinflation. Hence, end-inspiratory volume is the major determinant of ventilator-induced lung edema (75). Increasing V_T promotes edema formation at a given end-inspiratory pressure (and volume), whereas adding PEEP seems to slow the development of edema and diminish the severity of tissue injury, but it does not prevent the alterations in microvascular permeability (5, 88). On the contrary, when PEEP results in additional overinflation, there is greater edema (Figure 13).

Roles of the magnitude of airway pressure and lung volume changes, duration of ventilation, and animal size.

Possible pressure–volume threshold for edema and permeability alterations. There is no well-defined volume above which alterations appear as the lung is overexpanded. The presence of an airway pressure threshold is however suggested by some of the above studies on isolated lungs by Parker and colleagues (53) (*see* ISOLATED LUNGS) and by the work by Carlton and coworkers (27) in intact animals. Carlton and coworkers produced graded increases in V_T in lambs and studied their effect on lymph flow and protein concentration. Peak inspiratory pressure (and therefore V_T) was increased in three successive steps (each of 4 h) from baseline (16 cm H_2O) to 61 cm H_2O. There was no change in lymph flow or protein composition during the first two steps (33 and 43 cm H_2O peak inspiratory pressure). But there was a 4- to 6-fold increase in lung lymph flow at the highest peak inspiratory pressure (61 cm H_2O, which corresponded to a V_T of 57 ml/kg). Similarly, the lymph–plasma protein concentration ratio did not change until the highest peak inspiratory pressure was reached. It then increased significantly, indicating altered microvascular permeability. The investigators concluded that microvascular alterations occur above a pressure threshold at 43 to 61 cm H_2O, rather than gradually. However, they also suggested that microvascular permeability and protein sieving properties were

already altered at airway pressures below this hypothetical threshold. Indeed, the albumin–globulin ratio in the lymph became lower than in the plasma when peak airway pressure was only 43 cm H_2O, reflecting the loss of the capillary sieving properties. This may indicate that the actual threshold may be lower than reported in this study. Indeed, pulmonary edema has been regularly produced with airway pressure levels lower than those used in this study. A peak inspiratory pressure of only 30 cm H_2O was enough in small animals like rats that develop mechanical ventilation–induced lung edema much more rapidly (22). Similarly, intact rats developed moderate pulmonary edema after 1 h of mechanical ventilation with a V_T of 20 ml/kg BW (92). Consistent with the absence of a well-delimited pressure or volume threshold, Tsuno and coworkers (26) found that ventilating sheep with a peak inspiratory pressure of 30 cm H_2O for more than 40 h invariably resulted in increased wet lung weight and gross pathologic alterations. Finally, stable (2 h) isolated perfused rat lung preparations could not be obtained when peak airway pressure was above 13 cm H_2O (54) (a pressure level which nevertheless resulted in a greater inflation than in closed-chest animals).

Several important conclusions can be drawn from these findings. First, it is very difficult to examine separately the effects of a given regimen of pressure and volume during mechanical ventilation and those of time. Indeed, as discussed previously, ventilatory settings which seem safe for as long as several hours (27) may prove deleterious when ventilation is prolonged for up to 2 d (26). This is analogous to the administration of a toxin: both individual doses and repeated doses must be taken into account. This issue is further complicated by the influence of species size, the smaller species being more prone to VILI. For instance, the ratio of extravascular lung water to blood-free dry lung weight in open-chest dogs ventilated for 30 min with 64 cm H_2O peak pressure was only 28% greater than that of animals ventilated with low (22 cm H_2O) airway pressures, indicating mild edema (25). By contrast, it took only 2 min to obtain edema of roughly the same severity (17% increase in the extravascular lung water to blood-free dry lung weight ratio) in rats ventilated with 45 cm H_2O peak pressure (6). This increase reached 90%, indicating severe edema, when ventilation was continued for up to 20 min (5).

There are many other examples of the slower appearance of VILI in intact large animals. Carlton and coworkers (27) found an increase in the extravascular lung water to dry lung weight ratio of only 19% in intact lambs ventilated with 58 cm H_2O peak inspiratory pressure for 6 h. Microscopic examination was either normal or showed only mild perivascular edema, but no alveolar edema. Alveolar flooding occurred in sheep, but after 18 h of ventilation with a peak inspiratory pressure of 50 cm H_2O (93). Wet lung weight normalized for body weight was 189% that of normal lungs (values for normal lungs obtained from [26]). After 27 h of this ventilation, the lung weight was 236% that of normal lungs. Thus, whereas ventilation may produce severe edema in small animals in less than 1 h, ventilation for 24 h or more with similarly high airway pressures is necessary in larger animals. The reasons for these differences in sensitivity have not yet been explained. Their consequences will be discussed under MECHANISMS OF ALTERED PERMEABILITY.

These studies suggest that any pressure–volume threshold is probably low and that duration greatly influences the severity of ventilator-induced lung edema, in addition to the degree of distention.

Reversibility of limited abnormalities. Prolonged ventilation at high airway pressure results in substantial, probably irreversible, damage. For example, rats ventilated with intermittent positive pressure with 45 cm H_2O peak pressure for 20 min, which is relatively long for a small animal (*see preceding section*), were moribund and their lungs had lesions analogous to those found in severe ARDS (4, 5). Similarly, sheep subjected to 50 cm H_2O peak pressure ventilation (24) died within 48 h and piglets in which an acute lung injury was induced by high-pressure mechanical ventilation (66) showed diffuse alveolar cellular proliferation after several days of support by conventional mechanical ventilation. But the changes in permeability and the edema resulting from moderate insults may be reversible, as in certain types of permeability edema (56, 94). Carlton and colleagues (27) found that the lung lymph flow and lymph–plasma protein concentration ratio of lambs ventilated at 61 cm H_2O peak pressure for 4 h (a relatively short time for closed-chest large animals, as explained in the preceding section) and allowed to recover returned to normal, indicating reabsorption of excess pulmonary fluid. But the albumin–globulin ratio in the lymph remained below that in plasma during the 6-h recovery period, suggesting the persistence of some altered microvascular permeability. Rats subjected to 35 mm Hg peak inspiratory pressure mechanical ventilation for only 2 min developed mild permeability edema with significant increases in extravascular lung water, dry lung weight, and albumin distribution space (6). There appeared to be no macroscopic alveolar edema after such a short period of ventilation, but ultrastructural examination disclosed endothelial blebbing identical to that described after longer periods (6). Hence, microvascular abnormalities are almost immediate, at least in small animals. The epithelial lining fluid volume (calculated using a modification of the method of Rennard and coworkers [95]) and protein content were increased by 180% and 80%, respectively, and a few blood cells were found in lavage fluid, indicating alveolar hemorrhage. Some animals were allowed to recover for as long as 3 h (6). Both extravascular lung water and dry lung weight promptly returned to normal, indicating that reabsorption of edema can be very rapid. Edema reabsorption does not necessarily indicate restoration of normal alveolocapillary barrier properties, but the ^{125}I-albumin distribution space measured after the high-pressure ventilation period was normal, indicating no further altered albumin permeability. Extravascular lung water and epithelial lining fluid volume decreased in parallel, reflecting the resorption of the interstitial and alveolar edema. There were no marked changes in epithelial lining fluid protein content, reflecting the slower-than-water clearance of protein in alveolar edema fluid (96). Thus, very short periods of overinflation can profoundly affect microvascular permeability and deep lung fluid balance. Most of these lung fluid balance abnormalities are reversible within hours although recovery of normal alveolar homeostasis may be slower.

Low Lung Volume Injury

Healthy lungs tolerate mechanical ventilation with physiologic tidal volumes and low levels of PEEP for prolonged periods without any apparent damage. The terminal airways remain open even at end-expiration during the normal tidal cycle and close at lower volumes, near the residual volume. Moreover, healthy lungs do not seem to be damaged when terminal units are repeatedly opened and closed for short periods (1 h) by negative end-expiratory pressure (which nevertheless reduces compliance and alters gas exchange) (97). But mechanical ventilation, even without overinflation, may worsen any preexisting lung injury because of regional overinflation due to the shrinking of the injured lung and uneven distribution of its mechanical properties and because of the increased shear stress in terminal units due to the repeated opening and clos-

ing of small airways (these mechanisms will be detailed in the section entitled POSSIBLE MECHANISMS OF VENTILATION-INDUCED LUNG INJURY). This may have been the case in the work by Woo and Hedley-Whyte showing that closed-chest dogs ventilated with very large (50 ml/kg body wt) tidal volumes for 8 h had no discernible abnormalities, whereas severe pulmonary edema developed in open-chest animals after similar ventilatory settings (38). Besides the hemodynamic differences between the two situations, it is possible that the reduction of lung functional residual capacity in open-chest animals ventilated without PEEP caused cyclic collapse and opening of terminal airways and further damage during tidal ventilation. A recent study (98) confirmed that repeated collapse and reexpansion of surfactant-deficient terminal units during ventilation with negative end-inspiratory pressure for 3 h leads to severe functional (decreased compliance and arterial Pa_{O_2}) and histologic lung damage (bronchiolar epithelial necrosis and hyaline membrane formation).

Lower inflection point on lung pressure–volume curve and VILI. There may be an increase in trapped gas volume during pulmonary edema and acute lung injury, especially when surfactant properties are altered, because of instability of terminal units (99). In such conditions, the slope of the inspiratory pressure–volume curve of the respiratory system often changes abruptly at low lung volume. This change occurs frequently within the VT, reflecting the massive opening of previously closed units (Figure 14). This has been termed the "lower inflection point." Most clinicians are aware of the importance of this phenomenon in terms of arterial oxygenation, because setting PEEP above this inflection point usually results in a very abrupt decrease in shunt and increase in Pa_{O_2} (100–103).

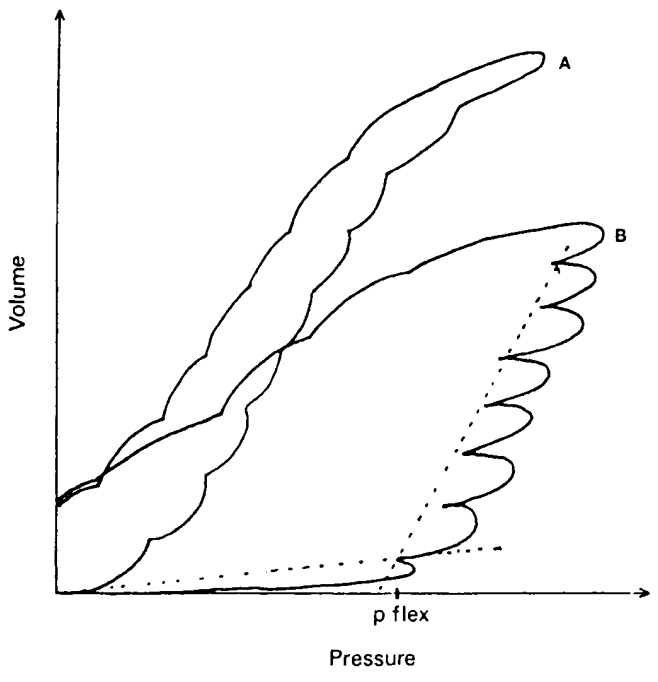

Figure 14. Pressure–volume curves of the respiratory system of closed-chest rabbits before (A) and after (B) surfactant depletion by repeated bronchoalveolar lavage. Compliance was markedly decreased after lung lavage. There was an abrupt change in the slope of the curve after a certain amount of pressure was applied (p flex), reflecting the massive opening of closed alveoli. Reproduced from Argiras and coworkers (28), with permission.

Attention has focused only relatively recently on the possibility that pulmonary lesions may be aggravated if this inflection point lies within the VT. Experimental evidence for this was initially provided by studies comparing conventional mechanical ventilation with high-frequency oscillatory ventilation in premature or surfactant-depleted lungs. More recently, studies performed during conventional mechanical ventilation of surfactant-depleted lungs with various levels of PEEP also provide support to the possibility that the repeated opening and closing of terminal units causes additional injury (28, 29, 31).

Effects of conventional mechanical ventilation and high-frequency oscillatory ventilation on premature and surfactant-deficient lungs. The search for a way of avoiding the large changes in pressure–volume generated by conventional mechanical ventilation, which could be responsible for additional lung damage, has led to the development of high-frequency oscillatory (HFO) ventilation. Studies on prematurely delivered lambs (104), baboons (105), and adult rabbits made surfactant-deficient by repeated saline lavage (106–108) indicate that the efficiency of HFO on lung lesions depends on the performance of a preliminary sustained static inflation (also called "lung conditioning") to recruit the greatest possible number of lung units before starting HFO (14).

Hamilton and coworkers (106) compared oxygenation and lung pathology in saline-lavaged rabbits ventilated by conventional mechanical ventilation with a 6 cm H_2O PEEP and HFO at similar mean airway pressure (15 cm H_2O). Both groups underwent static inflation at 25 to 30 cm H_2O for 15 s. HFO-treated animals had considerably higher Pa_{O_2}. More importantly, whereas conventionally ventilated rabbits had extensive hyaline membrane formation, the lungs of HFO-treated animals had few if any hyaline membranes.

Meredith and coworkers, working on premature baboons, showed that hyaline membrane disease was prevented when HFO was preceded by a recruitment maneuver (105). The importance of successful recruitment for preventing lung injury during HFO was illustrated by the severity of the changes in microvascular and alveolar permeability and histologic damage, which were similar to those caused by conventionally ventilating premature newborn lambs, when recruitment was not successful (104). Failure to achieve recruitment was ascribed to the inability of premature lungs to secrete enough surfactant (104).

Another study (107) also indicated the pivotal role of lung recruitment. Rabbits made surfactant-deficient (by repeated lung lavage) were subjected to conventional mechanical ventilation with a PEEP (8 cm H_2O) below the inflection point on the pressure–volume curve and a mean airway pressure of 18 to 19 cm H_2O, or to HFO at two levels of mean airway pressure (9–10 and 15–16 cm H_2O) resulting in low or high lung volumes. All animals underwent recruitment by static lung inflation at an airway pressure of 30 cm H_2O for 15 s, and were then connected to the conventional or HFO ventilator. Lung mechanical properties were better preserved in the HFO–high lung volume animals. Indeed, at the end of the experimental period (7 h) lung compliance was significantly greater in HFO–high-volume animals than in those ventilated with HFO–low-volume or conventional mechanical ventilation. Consequently, HFO–high-volume animals had a lung volume above FRC 3 times that of animals ventilated with HFO at low lung volume and 5 times that of animals conventionally ventilated. These preserved mechanical properties resulted in markedly better oxygenation. HFO–high-volume animals had also considerably less hyaline membrane and bronchiolar epithelium necrosis. This study suggests that reopening an atelectasis-prone lung is not sufficient to prevent injury due to shear stress when venti-

lation causes the repeated collapse and opening of terminal airways. It is thus important to keep the lung open (109) by applying sufficient mean airway pressure during HFO. Avoiding large pressure–volume variations with HFO does not totally prevent lung injury if sufficient FRC cannot be maintained.

The prevention of VILI by HFO was essentially demonstrated in the particular context of surfactant deficiency. Its efficiency during other types of lung injury is largely unknown (14, 110).

Importance of maintaining lung volume during conventional mechanical ventilation: Effect of PEEP. The hypothesis that maintenance of an "open lung" during the whole ventilatory cycle (109) by setting an appropriate level of PEEP prevents distal lung injury was also tested during conventional mechanical ventilation of diseased lungs.

Sykes and coworkers (28, 29) studied this issue ventilating rabbits whose lungs were depleted of surfactant by lavage. Peak inspiratory pressure was 15 mm Hg at the beginning of the experiment and 25 mm Hg at the end (5 h later), because lung compliance decreased (V_T was set but not stated). PEEP was adjusted so that FRC was either above or below the lower inflection point (*see* Figure 14 *for details*) on the inspiratory limb of the pressure-volume curve. This gave PEEP levels of about 1 to 2 mm Hg (below inflection) and 8 to 12 mm Hg (above inflection). The mortality rates in the two groups were identical, but the arterial Pa_{O_2} was better preserved and there was less hyaline membrane formation in the high PEEP group (28, 29). This lessening of pathologic alterations occurred even when the mean airway pressures in the low and high PEEP groups were kept at the same level by adjusting the inspiratory/expiratory time ratio (29). Muscedere and colleagues (31) recently reported similar results for isolated, unperfused, lavaged rabbit lungs ventilated with a low (5 to 6 ml/kg BW) V_T and with a PEEP set below or above the inflection point. However, Sykes and colleagues could not replicate these findings in rabbits with hydrochloric acid–injured lungs using the same ventilation settings (30). Whether the protective effect of PEEP during lung injury is restricted to the peculiar situation of surfactant depletion remains unsettled. A recent study in isolated rat lungs (which will be further discussed in the section on mediators) reported much greater increases in proinflammatory cytokines (tumor necrosis factor–alpha [TNFα] and interleukin-1β [IL-1β]) in bronchoalveolar lavage fluid when ventilation was conducted at low end-expiratory lung volume (without PEEP) than with PEEP (111).

It therefore seems likely that unstable lung units may be damaged by repeated opening and closing during tidal ventilation. PEEP may prevent diffuse alveolar damage during prolonged ventilation at high lung volume by stabilizing distal units. This may explain in part the preservation of alveolar epithelium integrity during high V_T mechanical ventilation in the presence of PEEP, as noted previously (5).

EFFECTS OF HIGH-VOLUME VENTILATION ON ABNORMAL LUNGS

Effects of High-volume Ventilation on Injured Lungs

Several investigators have evaluated the effect of acute overinflation on damaged lungs. All the studies agree that diseased lungs are very susceptible to the detrimental effects of mechanical ventilation.

Bowton and Kong (112) showed that isolated perfused rabbit lungs injured by oleic acid gained significantly more weight when ventilated with 18 ml/kg BW than when ventilated with 6 ml/kg BW V_T. Hernandez and colleagues (113) compared the effects of oleic acid alone, mechanical ventilation alone, and a combination of them both on the capillary filtration coefficient and wet-to-dry weight ratio of isolated perfused lungs from young rabbits. These measurements were not significantly affected by low doses of oleic acid, or mechanical ventilation with a peak inspiratory pressure of 25 cm H_2O for 15 min. However, the filtration coefficient increased significantly when oleic acid injury was followed by mechanical ventilation. The wet-to-dry weight ratio of these lungs was significantly higher than that of the lungs subjected to oleic acid injury or ventilation alone. The same group also showed that the increased filtration coefficient produced by ventilating isolated blood-perfused rabbit lungs with 30 to 45 cm H_2O peak pressure was greater when surfactant was inactivated by instilling sodium dioctyl succinate (114). Whereas light microscope examination showed only minor abnormalities (minimal hemorrhage and vascular congestion) in the lungs of animals subjected to ventilation alone, or surfactant inactivation alone, the combination of the two caused severe damage (edema and flooding, hyaline membranes, and extensive alveolar hemorrhage).

These results on isolated lungs suggest that VILI may develop at lower airway pressure in abnormal lungs. The situation in intact animals was investigated by comparing the effects of different degrees of lung distention during mechanical ventilation in rats whose lungs had been injured by α-naphthylthiourea (ANTU) (89). ANTU infusion alone caused moderate pulmonary edema of the permeability type, with only interstitial edema. Mechanical ventilation of intact rats for 2 min resulted in a permeability edema whose severity depended on the V_T, ranging from small (25 ml /kg BW V_T) to moderate (45 ml/kg BW V_T). Thus, it was possible to predict how much mechanical ventilation would injure lungs diseased by ANTU by summing up the separate increases in extravascular lung water, dry lung weight, or albumin distribution space produced by mechanical ventilation alone or ANTU alone (Figure 15a). The results showed that the lungs of the animals injured by ANTU ventilated at high volume (45 ml/kg BW) had more severe permeability edema than predicted (Figure 15a), indicating synergism between the two insults rather than additivity. Hence, abnormal lungs are more susceptible to the harmful effects of overinflation than normal lungs. Even minor alterations, such as those produced by spontaneous ventilation during prolonged anesthesia (which degrades surfactant activity and promotes focal atelectasis [115, 116]), are sufficient to synergistically increase the harmful effects of high-volume ventilation (Figure 15b) (89). The extent to which the lung mechanical properties have deteriorated prior to ventilation is a key factor in this synergy. The amount of edema produced by high-volume mechanical ventilation in the lungs of animals given ANTU, or that had undergone prolonged anesthesia was inversely proportional to the quasi-static compliance of the respiratory system measured at the very beginning of mechanical ventilation (first mechanical breaths), before it could cause any additional damage (Figure 16) (89). Thus, existing lung abnormalities of whatever severity may potentiate ventilation-induced injury. The reason for this synergy needs clarification. The presence of local alveolar flooding in animals given 45 ml/kg BW ventilation was the most evident difference from those ventilated with lower, less harmful, V_T (89). It is conceivable that flooding reduced the number of alveoli that received the V_T, exposing them to overinflation and rendering them more susceptible to injury, further reducing the aerated lung volume and resulting in positive feedback. The same reasoning applies to prolonged anesthesia, during which the aerated lung volume was probably gradually reduced by atelectasis (89). Both flooding and atelectasis decrease compliance, likely to an extent that is correlated with their spreading. It is thus not surprising

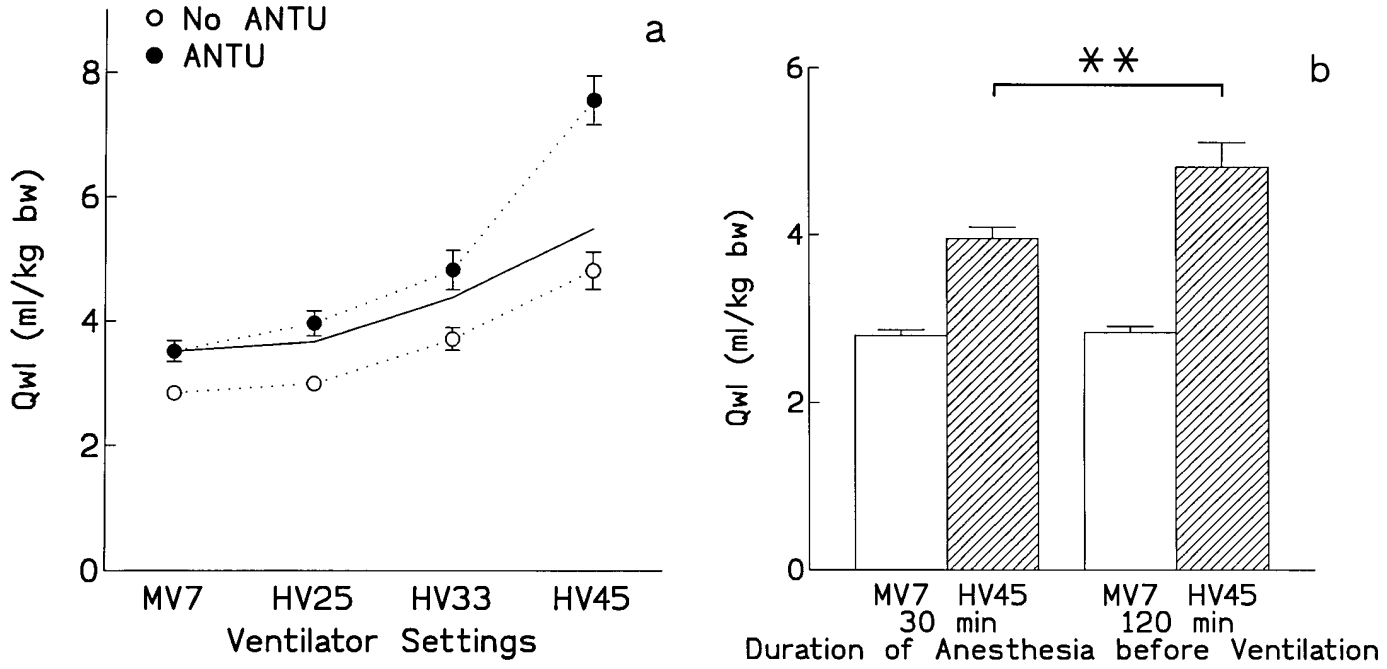

Figure 15. Interaction between previous lung alterations and mechanical ventilation on pulmonary edema: (*a*) Effect of previous toxic lung injury. Extravascular lung water (Qwl) after mechanical ventilation in normal rats (*open circles*) and in rats with mild lung injury produced by α-naphthylthiourea (ANTU) (*closed circles*). V_T varied from 7 to 45 ml/kg BW. The *solid line* represents the Qwl value expected for the aggravating effect of ANTU on ventilation edema assuming additivity. ANTU did not potentiate the effect of ventilation with V_T up to 33 ml/kg BW. In contrast, ventilation at 45 ml/kg BW V_T resulted in an increase in edema that greatly exceeded additivity, indicating synergy between the two insults. (*b*) Effect of lung functional alteration by prolonged anesthesia. Intact rats were anesthetized and breathed spontaneously for 30 or 120 min prior to mechanical ventilation with 7 ml/kg BW (*open bars*), or 45 ml/kg BW (*shaded bars*) V_T in intact rats. Qwl of animals ventilated with a high V_T was significantly higher than in those ventilated with a normal V_T. Qwl was not affected by the duration of anesthesia in animals ventilated with a normal V_T. In contrast, 120 min of anesthesia before high V_T ventilation resulted in a larger increase in Qwl than did 30 min of anesthesia (**$p < 0.01$). Reproduced from Dreyfuss and coworkers (89), with permission.

that the lower the lung distensibility before ventilation (as inversely reflected by quasi-static compliance, an index of the amount of lung that remains open), the more severe were the alterations induced by high-volume ventilation (Figure 16) (89).

Interaction between Severe Alveolar Flooding and Mechanical Ventilation

Uneven distribution of ventilation during acute lung injury (117) and severe alveolar flooding may render those lungs more prone to regional overinflation and injury. Preliminary results support this possibility (118). Alveolar flooding was produced by instilling 2 ml saline into the tracheas of anesthetized rats. The rats were then immediately ventilated for 10 min with V_T of up to 33 ml/kg. Flooding with saline per se did not significantly affect microvascular permeability as indicated by the similar extravascular lung distribution spaces of radiolabeled albumin in intact and flooded animals when the V_T was low. As V_T was increased the albumin distribution space became much larger in flooded animals, reflecting further impairment of their endothelial barrier. Flooding and mechanical ventilation acted synergistically to cause injury, probably because of regional overinflation in these lungs with very uneven mechanical properties. There was also a correlation between end-inspiratory airway pressure, the lower inflection point on the pressure–volume curve, and albumin distribution space in flooded animals ventilated with a high V_T (119). Thus, the less compliant and recruitable the lung was after saline flooding, the more severe were the changes in permeability caused by lung distention.

Effects of Resting the Lung on Ventilator-induced Lung Injury

The detrimental effect of mechanical ventilation on injured lungs has led to the hypothesis that "putting lung at rest" may be a safer way of management. HFO may allow resting the lungs by avoiding the large pressure–volume changes that occur during conventional mechanical ventilation. HFO can have beneficial effects on lung injury in the particular context of surfactant deficiency. Other techniques have been developed to rest the lungs, either by not ventilating them at all, or by using very-low-frequency ventilation, such as in extracorporeal membrane oxygenation (120) and extracorporeal CO_2 removal (13). There are few experimental data on the effects of lung rest during experimental lung injury.

Borelli and coworkers (93) compared continuous positive airway pressure breathing and extracorporeal CO_2 removal with conventional ventilation in sheep following moderate lung injury by high peak inspiratory pressure (50 cm H_2O) ventilation. Animals ventilated unconventionally had better outcomes, but there was no reduction in the wet lung weight. Hyaline membrane disease has been prevented in premature lambs by using apneic oxygenation with extracorporeal CO_2 removal (121). Fetal lambs were prematurely delivered and conventionally mechanically ventilated or oxygenated with continuous intratracheal oxygen (apneic oxygenation), while CO_2

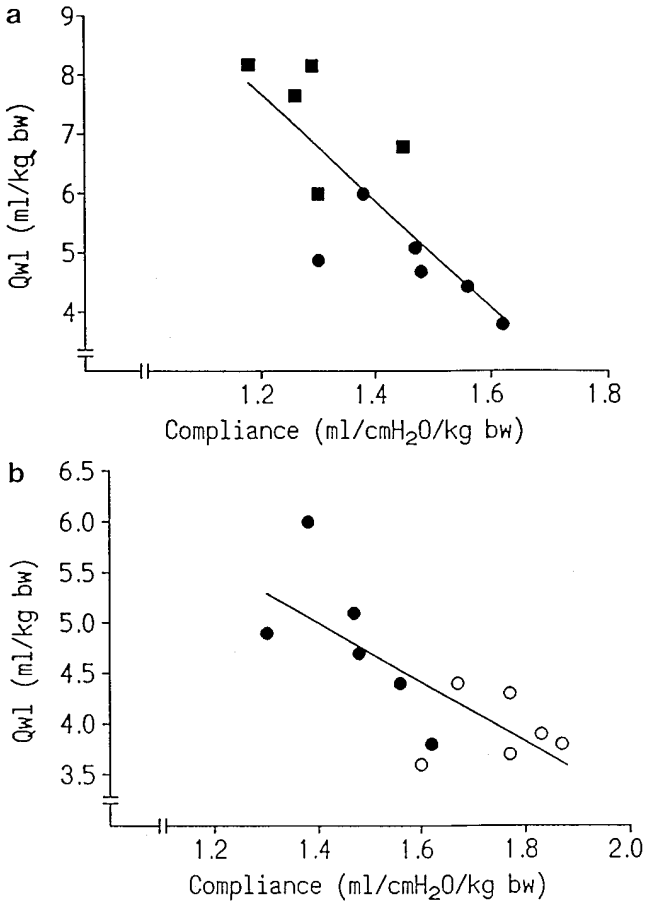

Figure 16. Correlation between Qwl measured after high VT ventilation (45 ml/kg BW) and quasi-static respiratory system compliance measured at the beginning of high VT ventilation in (*a*) anesthetized rats injected (*closed squares*) or not (*closed circles*) with ANTU before ventilation ($p < 0.01$), and (*b*) anesthetized rats that breathed spontaneously for 2 h (*closed circles*) or 30 min (*open circles*) before ventilation ($p < 0.01$). In both situations, a lower initial compliance was predictive of a larger amount of ventilation-induced edema. Reproduced from Dreyfuss and coworkers (89), with permission.

was removed with an extracorporeal membrane lung. Mortality was significantly lower in the animals treated with apneic oxygenation and extracorporeal CO_2 removal. Moreover, the lungs of conventionally ventilated animals contained extensive hyaline membranes, whereas those of the animals treated with apneic oxygenation did not. Similarly, Dorrington and coworkers (122) compared the effects of apneic oxygenation plus total extracorporeal CO_2 removal to those of conventional mechanical ventilation on the 6-h survival of rabbits with respiratory failure induced by saline lavage. Only one of the six conventionally ventilated rabbits survived, compared with five of six in the group treated with extracorporeal CO_2 removal. The sample was too small for this difference to be statistically significant. Nevertheless, histologic abnormalities seemed less severe in the animals treated by extracorporeal CO_2 removal. In contrast, Yanos and coworkers (123) did not find that such "resting" reduced pulmonary edema. They compared extravascular lung water in dogs with oleic acid–induced pulmonary edema that were ventilated at a low frequency and reduced VT plus extracorporeal membrane oxygenation, with the condition of the lungs of dogs conventionally ventilated for 5 h. Hypopnea had no beneficial effect on edema.

In conclusion, whether or not lung rest attenuates the severity of acute lung injury has yet to be clearly demonstrated. The above discussion nevertheless suggests that it is logical to avoid both the overstretching and cyclic closing and opening of terminal units.

POSSIBLE MECHANISMS OF VENTILATION-INDUCED LUNG INJURY

It is now clear that ventilation-induced pulmonary edema is essentially the result of severe changes in the permeability of the alveolar–capillary barrier. Small increases in microvascular transmural pressure may add their effects to those of altered permeability to enhance edema severity.

Depending on the duration of the aggression, two different kinds of injury probably occur. Small animals very rapidly develop a severe permeability pulmonary edema as a consequence of acute extreme lung stretching (this will be further examined in the discussion of mechanical effects of ventilation). This edema probably does not involve inflammatory cell recruitment or secretion of mediators. Edema develops more slowly in larger animals, in particular in response to moderately high airway pressures, rendering the situation more complex. A low lung volume injury probably adds its own effects to the direct mechanical aggression at high end-inspiratory volume. Indeed, as explained earlier, high VT mechanical ventilation without PEEP may reduce the aerated volume and gradually cause mechanical nonuniformity. This lung inhomogeneity will in turn promote overinflation of the more distensible and probably healthier zones, leading to positive feedback aggravation. In addition, lung injury develops slowly enough in large animals for inflammatory pathways to become involved.

Mechanisms of Increased Vascular Transmural Pressure

Increased fluid filtration by this mechanism may occur at both extra-alveolar (33, 34) and alveolar (124–126) sites during mechanical ventilation. Increased transmural pressure in extra-alveolar vessels may result from the increase in lung volume, a consequence of lung interdependence (35, 127, 128), whereas increased filtration across alveolar microvessels may be the consequence of surfactant inactivation (22, 126).

Increased transmural pressure in extra-alveolar vessels. The interdependence phenomenon is the consequence of the lung architecture (39): the outside wall of one airspace is the inside wall of its neighbor. Thus, each structure exerts traction forces on and receives them from adjacent structures. The principal result of lung interdependence is to maintain uniform expansion of airspaces. In uniformly expanded lungs, the effective pressure distending airspaces is close to transpulmonary pressure. In contrast, nonuniform lung expansion results in local distending pressures that differ from transpulmonary pressure in a direction and magnitude so as to oppose nonuniformity. As discussed previously, this may result in considerable regional stress. As lungs are inflated, an outwardly directed force stretches the connective network and decreases the pressure in the interstitial space surrounding extra-alveolar vessels. Their transmural pressure increases (assuming that the luminal pressure remains constant), leading to their expansion (35, 127). It has been calculated that, in fact, the increase in extra-alveolar vessel diameter during lung inflation can be accounted for by an outward-acting pressure, whose changes are larger in absolute value than those of pleural pressure (1 to 2 cm H_2O per cm H_2O increase in transpulmonary pressure [128]). This boosting effect is the consequence of the conver-

gence of the lung connective network from the entire visceral surface to the more reduced surface of the extra-alveolar vessels, resulting in increased radial traction on these vessels. As stated by Howell and colleagues (127): "when the alveoli are inflated, the alveolar pressure is acting on a larger area at the surface of the lung unit than at the central blood vessel wall. Therefore, the total force (pressure × area) acting outwards is greater than that acting inwards, and the resulting outward movement of the surface of the lobule will pull the blood vessel wall outwards."

The interdependence between blood vessels and surrounding lung parenchyma is especially relevant to the context of mechanical ventilation because of the contribution of filtration across extra-alveolar vessels during edema formation. This important role has been demonstrated in excised lungs (33) and lungs *in situ* in open-chest animals (129). Raised alveolar pressure and extension of zone 1 conditions accelerated the development of hydrostatic pulmonary edema in dog lobes (34). The edema fluid probably leaked from extra-alveolar vessels, because there was no flow in capillaries under such conditions. The rate of edema formation was correlated with the alveolar pressure and, therefore, with the magnitude of distention (Figure 17).

Enhanced filtration across extra-alveolar vessels may partly explain why PEEP enhanced edema formation when the VT was kept constant (resulting in increased end-inspiratory volume) in isolated perfused lobes (79, 80). Indeed, although PEEP probably tended to decrease perfusion by inflating the lungs and placing them under zone 1 conditions, the increase in lung volume might have favored extra-alveolar vessel transudation. As already discussed, this PEEP-mediated increase in fluid filtration has been observed essentially in isolated lungs with perfusion kept constant (79, 80). The situation is different in closed-chest animals, in which the less important inflation and the decrease in cardiac output resulting from raised intrathoracic pressure probably account for the lack of

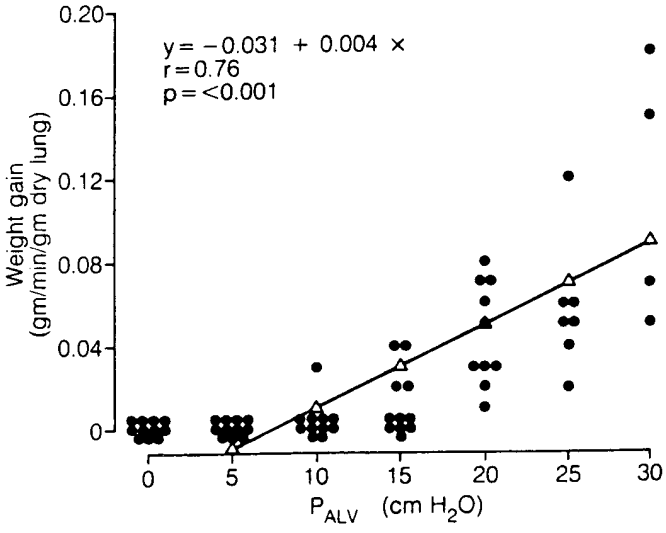

Figure 17. Relationship between alveolar pressure and rate of hydrostatic edema formation in *in situ* lobes of open-chest dogs. Pulmonary arterial and venous pressures were kept at 1 cm H_2O. When lung volume was low (alveolar pressure of 10 cm H_2O) no edema occurred, whereas greater distensions produced a linear increase in lung weight gain, indicating edema formation. Reproduced from Albert and coworkers (34), with permission.

effect of PEEP on edema formation (35, 83–85), except when the increase in end-inspiratory volume was such as to cause additional VILI (86).

Increased transmural microvascular pressure probably contributes to edema formation during VILI. The magnitude of its contribution remains a matter of speculation. Clearly, the moderate increases in transmural pressure (measured by several investigators [25, 27]) cannot account for the severity of the changes in permeability. However, important regional stress may develop during inflation of nonuniform lungs and result in increased microvascular transmural pressure large enough to cause pore stretching (40, 41, 130, 131) or capillary stress failure (42), as will be discussed in the section entitled MECHANICAL EFFECTS OF VENTILATION.

Increased transmural pressure in alveolar vessels. Mechanical ventilation may inactivate surfactant and increase alveolar surface tension. Faridy and colleagues (132) showed that the pulmonary pressure–volume curves of excised dog lungs were altered by mechanical ventilation. They found an increase in the surface tension of extracts of these lungs that correlated with VT and ventilation time. McClenahan and Urtnowski reported similar findings for excised rat lungs (133). These abnormalities were attributed to depletion of surfactant, or alteration of its surface properties. However, studies on open-chest cats (134), closed-chest rabbits (135), and isolated perfused rat lungs (136) all showed that ventilation increases surfactant release. It is thus possible that the decrease in surface activity was not due to surfactant depletion, but to its inactivation because of the low lung volume and low alveolar surface area at end-expiration in these lungs: the surfactant released by mechanical ventilation could not spread readily over this reduced surface and was inactivated by compression (134). It has been shown that a surface film from lung extracts could be reversibly compressed to 50% of its initial area, after which any further compression causes rupture of the film on reexpansion (137). An alternative explanation is that surfactant might be lost in the airways at end-expiration (138). The abnormal surface tension was reversed when the lung volume was maintained constant. This restoration of surfactant properties was probably the result of an active process (*de novo* production or secretion of surfactant) because it was inhibited by cooling or the absence of oxygen (132, 133). Surfactant dysfunction during mechanical ventilation–induced edema might also have occurred because of inactivation by plasma-derived proteins, in particular fibrin, as this has been observed in several models of permeability edema (139–141).

Surfactant inactivation should increase the alveolar surface tension and decrease the negative pressures surrounding the alveolar vessels, thereby increasing transmural pressure and fluid filtration. This was suggested by Pattle and Clements (124, 125) and tested in open-chest dogs by Albert and coworkers (126). They observed that the isogravimetric pressure (the vascular pressure at which the net fluid flux from pulmonary vessels is zero) was lower when lungs were cooled or ventilated at a low resting volume, conditions known to inactivate surfactant. The authors interpreted this fall in isogravimetric pressure as indicating easier extravasation, reflecting a decrease in perimicrovascular pressure (126).

Application of PEEP preserves surfactant function by two putative mechanisms both related to maintainance of an elevated end-expiratory lung volume: avoiding surface film collapse and subsequent inactivation during reexpansion from a low lung volume (132, 134), and prevention of surfactant loss in the airways (138). Together with the already discussed effects of PEEP on fluid filtration, preservation of surfactant properties probably explains in part why PEEP reduced edema

formation in experiments performed at constant end-inspiratory volume (5, 22, 88).

Mechanisms of Altered Permeability

While permeability alterations are obvious and severe during ventilator-induced edema, the underlying mechanisms are not fully understood, and there are probably several. In particular, as previously stressed, the mechanisms of lung injury may well vary according to the extent and duration of lung overdistension.

Effects of surfactant inactivation. In addition to its effects on fluid filtration, surfactant inactivation and elevated alveolar surface tension may increase alveolar epithelial permeability to small solutes. DTPA clearance in rabbits (142) and dogs (143) was increased following surfactant inactivation by detergent aerosolization. This effect was ascribed to the uneven distribution of lung mechanical properties resulting in ventilation inhomogeneities and regional overexpansion, rather than to the elimination of peculiar barrier properties of surfactant (143). The effects of surfactant inactivation and large VT ventilation on alveolocapillary permeability (as assessed by pulmonary DTPA clearance) are additive (144). Increased surface tension may also alter endothelial permeability as a result of increased radial traction on pulmonary microvessels (126). The effects of surfactant inactivation on the microvascular endothelial barrier properties have not been unambiguously characterized. Experiments were conducted in dogs (145) and sheep (146) given aerosolized detergent. Microvascular permeability was assessed by analysis of lymph-to-plasma protein ratio during hydrostatic edema caused by increased pulmonary venous pressure. Bredenberg and colleagues found that this ratio fell, indicating an unchanged protein reflection coefficient (145), whereas Wang and coworkers reported that this ratio was unchanged, indicating increased microvascular permeability to proteins (146). The reasons for these discrepancies were unclear. Finally, surfactant inactivation may result in a transient, moderate (+50%) increase in the capillary filtration coefficient (114).

Participation of inflammatory cells and mediators.

Role of inflammatory cells. The endothelial cell disruptions that have been observed during overinflation edema in small animals may allow direct contact between polymorphonuclear cells and basement membrane (Figure 8). This contact may promote leukocyte activation. As previously mentioned, the short duration of experiments conducted in small animals did not allow massive leukocyte recruitment. A striking feature of the VILI that occurs after several hours in larger animals is the infiltration of inflammatory cells into the interstitial and alveolar spaces. In one of the earliest studies on this subject, Woo and Hedley-Whyte (38) observed that overinflation produced edema in open-chest dogs, and that leukocytes accumulated in the vasculature and macrophages in the alveoli. These findings were confirmed and extended by Tsuno and coworkers, who observed interstitial lymphoid infiltration and alveolar macrophage and neutrophil infiltration in the lungs of piglets ventilated at high VT for 22 h (66). Raising alveolar pressure with PEEP during mechanical ventilation markedly increases the transit time of leukocytes in the lungs of rabbits (147) and in humans (148). Granulocyte–endothelial cell interactions may also increase microvascular permeability. Rabbits depleted of surfactant by lavage were used by Kawano and colleagues (67) to show that neutrophil-depleted animals had preserved gas exchange, little lung albumin leakage, and no hyaline membranes after 4 h of conventional mechanical ventilation, whereas undepleted animals had severe hypoxemia, marked albumin leakage, and extensive hyaline membrane formation. Sugiura and coworkers (108) also showed that the ventilator pattern has a marked influence on neutrophil influx and activation in the same model. Conventionally ventilated animals had more lung neutrophils, and these neutrophils produced more reactive oxygen species than did those of animals ventilated with HFO following a recruitment maneuver. Similarly, Matsuoka and colleagues (149) and Imai and colleagues (150) observed that more granulocytes were recovered from surfactant-depleted rabbits by bronchoalveolar lavage after 4 h of conventional mechanical ventilation than after HFO. The respiratory burst activity of the granulocytes recovered from conventionally ventilated animals was lower than that of granulocytes from HFO animals, suggesting previous activation (149).

Mediators. The implication of thromboxane A2 and prostacyclin in the modulation of vascular resistance during high-inflation edema has been considered by several investigators. Bowton and Kong (112) found no difference in the amounts of thromboxane B2 (the stable metabolite of thromboxane A2) in the perfusates of oleic acid–injured isolated rabbit lungs ventilated with high and low VT. Parker and coworkers (25) reached a similar conclusion for both thromboxane and prostacyclin. Similarly, Imai and coworkers (150) reported that the amounts of 6-keto-PGF1α (the stable metabolite of prostacyclin) in the bronchoalveolar lavage fluid from conventionally ventilated and HFO-ventilated animals were similar. In contrast, the same authors found that the bronchoalveolar lavage of surfactant-depleted rabbits conventionally ventilated contained more platelet-activating factor and thromboxane B2 (150) than the lavage from rabbits ventilated with HFO. Similar results for platelet activating factor were obtained in premature baboons (105). In summary, the precise contribution if any, of cyclo- or lipoxygenase products to the genesis of VILI remains to be evaluated. The possible involvement of metalloproteinases during VILI was recently suggested by the finding of an increased lung content of gelatinase A and collagenase messenger RNAs (mRNAs) in rats mechanically ventilated for 25 min with 35 cm H_2O peak airway pressure (151).

The participation of inflammatory cytokines in the course of VILI has been the subject of recent studies. Narimanbekov and Rozycki found that recombinant IL-1 receptor antagonist (IL-1ra) decreased the severity of lung injury produced by hyperoxia and ventilation with a 24 cm H_2O peak inspiratory pressure for 8 h in surfactant-depleted rabbits (152). The animals that were given IL-1ra had lower albumin and elastase concentrations in the lavage fluid and fewer neutrophils in their lungs. Recently, Tremblay and colleagues (111) examined the effects of different ventilatory strategies on the concentrations of several cytokines in bronchoalveolar lavage fluid of isolated rat lungs ventilated with different end-expiratory pressures and VT. High VT volume ventilation (40 ml/kg BW) with zero end-expiratory pressure resulted in considerable increases in TNF-α, IL-1β, and IL-6 and in MIP-2, a chemokine of the IL-8 family (Figure 18). Stretching A549 cells, a human alveolar type II cell line, induced the release of IL-8 (153), but ventilation with a 10 cm H_2O PEEP and the same end-inspiratory volume (and thus a lower VT) resulted in the release of less inflammatory cytokines in the alveolar space (Figure 18). Northern blot analysis of lung tissue extracts revealed a similar pattern for c-*fos* mRNA (transcription of the c-*fos* gene is one of the earliest nuclear responses to several stimuli, including cell stretch). However, the observations by Tremblay and colleagues were obtained in isolated nonperfused lungs ventilated for 2 h. The ventilatory settings that produced major cytokine increases (40 ml/kg BW VT, no PEEP) killed intact rats in less than 1 h (4, 5, 22). The influence of ventilation strategy on cytokine production was further demonstrated in a recent

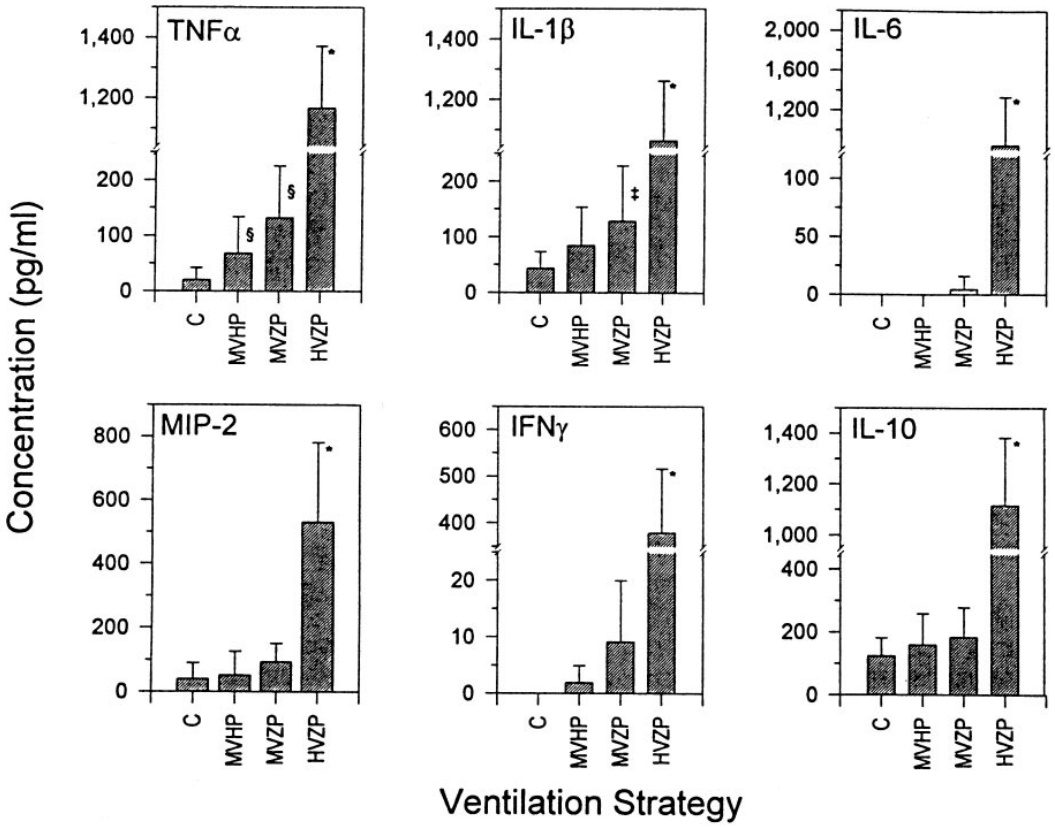

Figure 18. Effect of different ventilatory strategies on cytokine concentrations in lung lavage of isolated unperfused rat lungs. Four ventilator settings were used: controls (C = normal V_T), moderate V_T + high PEEP (MVHP), moderate V_T + zero PEEP (MVZP), high V_T + zero PEEP (HVZP) resulting in the same end-inspiratory distension as MVHP. Major increases in cytokine concentrations were observed with HVZP. Reproduced from Tremblay and coworkers (111), with permission.

study by Takata and coworkers (154). There were large increases in TNF-α mRNA in the intra-alveolar cells of surfactant-depleted rabbits after 1 h of conventional mechanical ventilation with peak inspiratory and end-expiratory pressures of 28 and 5 cm H_2O (resulting in a mean airway pressure of 13 cm H_2O). Ventilation with HFO for a similar duration and at the same mean inspiratory airway pressure produced minimal increases in TNF-α gene transcripts. The presence of these inflammatory mediators in lungs subjected to high-volume ventilation is in keeping with the well-documented recruitment of neutrophils that occurs after long-term ventilation (66, 108, 149, 150).

In addition to increasing the amount of cytokines in the lung, overinflation during mechanical ventilation may promote the release of cytokines into the blood. This very interesting observation on isolated ventilated and perfused mouse lung was reported by von Bethmann and coworkers (155, 156). Both TNF-α and IL6 were released into the perfusate when lungs were ventilated with a high V_T with intermittent negative (−25 cm H_2O) pressure. Such a loss of compartmentalization has also been described in other types of lung injury (157) and might play a role in the genesis of multiple organ failure, which may occur following acute lung injury in humans (158). Systemic cytokine activation might also result from the translocation of bacteria from the lungs. Nahum and coworkers (159) observed the occurrence of bacteremia during overdistension and tidal closure and reopening of infected lungs. They studied the influence of mechanical ventilation strategy on the diffusion of *Escherichia coli* from the lung into the bloodstream after tracheal instillation in dogs. Blood cultures were positive in five of six dogs mechanically ventilated with a very high V_T (76 ml/kg) and a 3 cm H_2O PEEP, whereas bacteria were found in the blood of only one of six dogs ventilated at the same end-inspiratory transpulmonary pressure (35 cm H_2O) but with a V_T of 47 ml/kg BW and a 10 cm H_2O PEEP, and in the blood of none of the dogs ventilated with a V_T of 15 ml/kg BW and a 3 cm H_2O PEEP.

Mechanical deformations during high airway pressure ventilation may produce various cellular effects. Tissue stretch may result in direct damage (the extreme limit being ruptures as during the classical barotrauma). More subtle events may also occur, including the triggering of inter- and intracellular signals. Preliminary results have shown that the inhibition of phosphotyrosine phosphatase (phosphorylation of tyrosine in adhesion proteins is associated with the release of cell–matrix adhesions) results in a greater increase in the capillary filtration coefficient during ventilation of isolated rat lungs with high airway pressure (160). This suggests that the increase in microvascular permeability may not be a simply passive physical phenomenon (a "stress failure" [61]), but the result of biochemical reactions. The strain produced by large lung volumes may initiate signal transduction pathways that depend on the cell type. In fetal lung cells, mechanical stress resulted in the activation of a tyrosine kinase and phosphorylation and activation of phospholipase Cγ, with increases in the inositol trisphosphate and diacylglycerol contents (162). Increases in these

second messengers have also been reported in endothelial cells in responses to cyclic strain (163). Cyclic deformation of endothelial cells promoted the secretion of the chemokine monocyte chemotactic protein-1 (164), an effect mediated by the opening of stretch-activated calcium channels and the release of calcium from intracellular stores. Mechanical deformation of endothelial cells induced oxidant stress and the release of H_2O_2 (165). Pulsatile stretch of fetal lung cells increased their cyclic AMP (cAMP) content and leads to the production of prostacyclin within 15 min (166). Ventilation at increased lung volume by a 20 cm H_2O continuous positive airway pressure (CPAP) also increased the cAMP content and protein kinase A activity of isolated rat lungs within 40 min (167). Mechanical stress may also elicit protective responses. High lung inflation was found to increase the expression of genes encoding lung extracellular matrix components and growth factors, suggesting that remodeling occurs rapidly in response to increased tissue strain (168). These observations suggest that high-volume ventilation may produce effects via autocrine and paracrine signaling, but the role of these pathways and mediators in the genesis of or resistance to VILI is unknown.

The local tissue distortion and zone 1 conditions that occur during high-pressure ventilation may affect the pattern of vascular resistance and perfusion. This nonuniformity would increase blood flow and endothelial shear stress in the regions where there is still perfusion, and these factors stimulate the release of NO by endothelial cells (169). Several reports have examined the influence of lung distention on lung NO production. Increasing FRC by imposing PEEP produced an increase in expired NO in isolated rabbit lungs (170), and in anesthetized rabbits (171). It is unclear whether this NO production is the consequence of tissue deformation or the redistribution of blood flow. Atrial natriuretic factor (ANF) relaxes the pulmonary vasculature and modulates lung microvascular permeability (172). Physiologic concentrations of ANF may protect against pulmonary edema by stimulating cyclic guanosine 3′, 5′-monophosphate (cGMP) accumulation in endothelial cells, which reduces free cytoplasmic calcium, stabilizing the cytoskeleton and tight junctions between cells. But higher concentrations of ANF cause protein leakage (172). ANF is synthesized by the lung parenchyma and the pulmonary veins (172). The inhibition of ANF secretion by compressed atria during mechanical ventilation, in particular with PEEP, is well documented and contributes to the water and sodium retention frequently observed in these patients (172, 173). However, ventilation with a large volume may stimulate the release of natriuretic factors from the pulmonary vessels undergoing increased stretch (especially cerebral natriuretic peptide which is also synthesized by pulmonary endothelial cells [174]). These may act as autocrine–paracrine factors to modulate pulmonary vascular resistance and permeability (the lung contains ANF receptors with guanylyl cyclase activity [175]). Cyclic GMP, which is implicated in the response to both NO and natriuretic factors, accumulated in the lung *in vivo* (176) and was released into the perfusate when isolated lungs were ventilated with high peak pressures (177). The nature of the pathways involved in this cGMP production and release and the significance of these observations certainly deserve investigation.

Mechanical effects of ventilation. As stated earlier, leukocyte activation and the action of humoral mediators are unlikely to explain the very fast onset of severe changes in permeability and lung ultrastructural damage after mechanical ventilation with high pressure–high volume in small animals (4, 6, 22). Direct mechanical injury is more likely to cause these rapidly developing abnormalities.

Diseased lungs with a patchy distribution of lesions may be subject to much greater regional stress than uniformly inflated lungs. A premonitory statement was made by Jere Mead and his colleagues when they studied the stress distribution in a model of heterogeneous lungs: "Mechanical ventilators, by applying high transpulmonary pressure to the nonuniformly expanded lungs of some patients who would otherwise die of respiratory insufficiency, may cause the hemorrhage and hyaline membranes found in such patients' lungs at death" (39) (the implications of this study have already been mentioned and are further discussed below). Thus, a moderate V_T may produce focal overinflation in these lungs if the amount of the almost normal and most compliant parenchyma is sufficiently reduced. Considerable pressures and shear forces may develop at specific points during the inflation of nonuniform lungs (39). Mead and colleagues calculated the pressure tending to expand collapsed areas may be considerable: a fully expanded lung surrounding an atelectatic region would be stretched by approximately 140 cm H_2O when the transpulmonary pressure is 30 cm H_2O (39). The tissue stress in these regions may exceed that produced by inflating normal lungs to near total lung capacity, a condition known, when repeated, to result in pulmonary edema (4, 22, 24).

A vicious cycle could be set up during VILI, with surfactant inactivation as the primary event followed by the development of atelectasis. The shear forces applied to adjacent zones may produce further damage, which will in turn further aggravate any mechanical inhomogeneity. The repeated opening and closing of distal units which may occur at both low and high lung volumes under such circumstances may also make lesions more severe by shearing off epithelial layers. These lesions may be lessened by stabilizing terminal units with PEEP above the inflection point on the pressure–volume curve (28, 29, 31). PEEP can also preserve epithelial integrity during high-volume edema (5), perhaps by a similar mechanism and/or because PEEP opposes alveolar flooding (81, 82), preserving surfactant from inactivation by plasma-derived proteins (140). This putative sequence of events is summarized in Figure 19.

A preliminary report suggesting predominance of lesions in dependent zones in large animals (dogs) further supports the role of mechanical factors during ventilator-induced lung injury (178). This distribution of lesions may be due to larger blood flow and hydrostatic pressures in dependent zones favoring edema formation and hemorrhage. Airway spaces in dependent zones that are more prone to flooding may undergo repeated opening and closing more easily during mechanical ventilation and be subjected to higher shear forces and hence lesions in terminal units. Similarly, ventilating animals prone (which results in a more uniform distribution of pleural pressure and edema fluid thus probably avoiding regional flooding) seemed to abolish the preferential distribution of lesions (179). Moreover, there were fewer histologic abnormalities in dogs with preinjured lungs (intravenous infusion of oleic acid) ventilated with large V_T in the prone position than in those ventilated in the supine position (180).

Improving the mechanical properties of diseased lungs may lessen the severity of VILI. A preliminary report has indicated that tracheal instillation of perfluorocarbon (which has tensioactive properties) decreased the severity of microvascular permeability alterations during lung injury produced by alveolar flooding with saline and high-volume ventilation in rats (119).

The lack of any clear demonstration that inflammatory cells and mediators are involved in the genesis of the acute microvascular permeability defect that occurs during lung distention, especially in small species (4, 6, 22), also suggests that mechanical factors play an important role. Moderate increases in microvascular hydrostatic pressure such as those measured

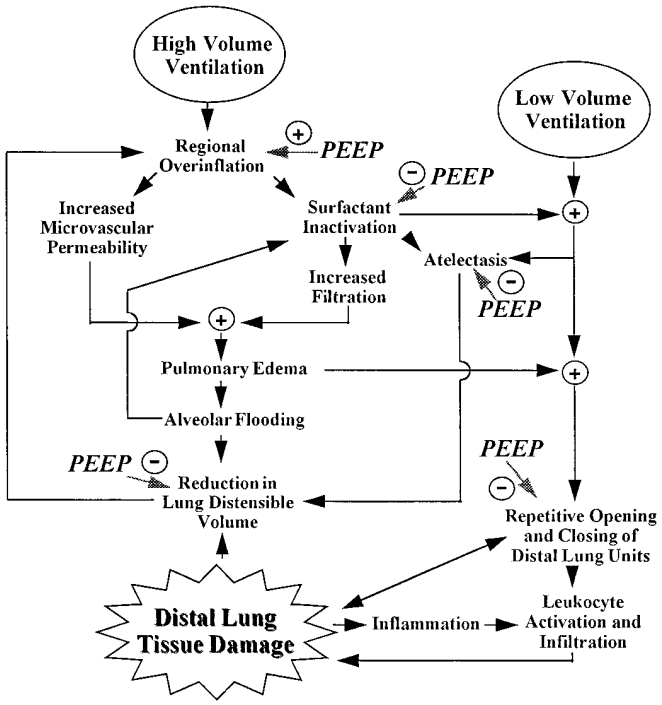

Figure 19. Flow diagram summarizing the contributors to mechanical ventilation–induced lung injury. PEEP generally opposes injury or edema formation (*minus sign*) except when it contributes to overinflation (*plus sign*).

during ventilator-induced lung injury are usually not considered to be responsible for ultrastructural abnormalities (7, 69, 73). Moreover, as mentioned previously, recent studies on isolated rabbit lungs with hydrostatic edema produced by 14 to 29 mm Hg increases in capillary pressure have shown bleb formation and breaks in the epithelial type I cell layer, but only rare microvascular alterations (70, 71).

The inflation of lungs with nonuniform mechanical properties may theoretically lead to very important increases in vascular transmural pressure in regions that are subjected to abnormally high outward-acting stress (39). Ultrastructural abnormalities of the alveolocapillary barrier have been described recently in lungs submitted to very high perfusing pressures (42, 181–184). West and colleagues (42, 181, 183) have shown that capillary pressures of 52.5 cm H_2O consistently disrupted the endothelial layer in isolated rabbit lungs with denudation of the basement membrane, blebbing of the alveolar epithelium, and breaks in the alveolocapillary barrier that allowed red blood cells to enter alveoli. These alterations have been linked to the mechanical failure of certain cell components in response to stretch and are called "stress failure." They explain the increase in microvascular permeability that occurs when the microvascular pressure is very high (130, 131), the so-called stretched pore phenomenon (40, 41). The above pressures must be considered as rough estimates, because there are major differences in susceptibility of species: dog lungs, for example, are more resistant to capillary stress failure than are rabbit lungs but less than horse lungs (184, 185).

Mechanical ventilation–induced lung injury and capillary stress failure have some similarities. Both ventilation-induced injury and stress failure may produce breaks in the alveolocapillary barrier leading to alveolar hemorrhage (4–6, 181, 183). They also appear to be rapidly reversible, as long as there is no cell lysis. Just as albumin leakage from capillaries ceased almost immediately after high-volume ventilation was stopped (6), the number of endothelial and epithelial breaks diminished when capillary pressures were returned to normal after being increased to a level that caused stress failure (186). This is also consistent with the normalization of microvascular permeability after microvascular pressure was returned to normal (40, 41). Lastly and more importantly, capillary stress failure is strongly influenced by lung volume: increasing lung volume by increasing transpulmonary pressure from 5 to 20 cm H_2O at a capillary transmural pressure of 32.5 cm H_2O resulted in a significant increase in the number of endothelial and type I epithelial breaks (182). The increase in the number of breaks produced by equivalent increases in transpulmonary pressure and capillary transmural pressure were similar. Thus, vascular pressures too low to affect microvascular permeability at low lung volume may increase microvascular permeability when the lung volume is sufficiently increased. West and coworkers proposed that overinflation edema might be the consequence of capillary stress failure, large lung volume being equivalent, in terms of tissue stress, to high capillary transmural pressure (42). This hypothesis is supported by the observation that smaller animals are more sensitive to both ventilator-induced lung injury (4, 6, 24, 25) and capillary stress failure (184, 185) than are larger ones.

But the increase in the number of endothelial and epithelial breaks observed at high compared with low lung volume was not significant at very high transmural microvascular pressure (52 cm H_2O) because of the important and unexplained variability of the number of breaks (182). Besides, there are notable differences between capillary stress failure and ventilator-induced lung edema. First, endothelial blebbing is the most often observed ultrastructural abnormality during overinflation edema but has never been reported during capillary stress failure (181, 183), even in intact animals such as horses suffering from exercise-induced lung hemorrhage, a disorder caused by excessively high pulmonary capillary pressure and regional lung volumes (187). Another difference is the presence of epithelial cell swelling and lysis and hyaline membrane formation when ventilation is sufficiently prolonged (4, 5). These abnormalities were not observed during capillary stress failure, perhaps because experiments were performed during static inflation only. In contrast to the crucial effect of duration of ventilation in determining the severity of ventilator-induced pulmonary edema (4, 6, 22), prolonging perfusion at high pressure did not increase the incidence of stress failure in isolated rabbit lungs (188). The ultrastructural peculiarities of overinflation edema together with the worsening of the lesions with time may be due to the specific effect of ventilation, which may cause injury both by overstretching and the cyclic closing and opening of terminal units. Differences between static and tidal inflation may also explain the finding of moderately increased epithelial permeability during static distention of whole lungs (48–50), whereas mechanical ventilation produces severe diffuse alveolar damage (4, 5).

The link between VILI and capillary stress failure is mainly speculative, although it may seem logical that they constitute two related manifestations of lung mechanical failure. In particular, the differences in the ultrastructural damage (lack of endothelial cell blebbing, and of type I cell lysis during capillary stress failure) require clarification.

The above mechanisms may interact to generate VILI. It is clear that the rapid onset of severe edema and cell changes in the response to high-volume ventilation is best explained by mechanical phenomena like surfactant inactivation and stress failure. Alveolar flooding, lung nonuniformity, and terminal airway closing and reopening further aggravate injury. Neutro-

phils are later activated and recruited in response to anatomic alterations (cellular destructions and basement membrane denudation [Figure 8]) and the release of inflammatory mediators. The effects of activated granulocytes may exacerbate those of mechanical stress to produce the full pattern of ventilator-induced lung injury (Figure 19).

CLINICAL RELEVANCE

Although these experimental findings on ventilator-induced microvascular injury have not yet been unequivocally shown to have clinical relevance, clinicians are becoming increasingly concerned about the potentially harmful effects of mechanical ventilation. As long ago as 1975, it was suggested that very high levels of PEEP should be viewed as a "fundamental means of aborting or reversing the primary pathophysiologic processes producing acute respiratory failure" (189). Ten years later, the risks associated with such PEEP levels were pointed out (190). And it has now been shown that even low PEEP levels may result in overdistension in some ARDS patients (191). Similarly, high tidal volume mechanical ventilation was standard practice for many years (192). This view has been challenged by the many recent studies discussed subsequently. Hence, pulmonary edema and lung injury during mechanical ventilation are the consequence of "volutrauma" rather than "barotrauma" (5, 75).

Acute lung injury is a nonuniform process (193, 194) which results in the uneven distribution of ventilation. Gattinoni and colleagues (194) have shown that ARDS lungs include healthy tissue, recruitable tissue, and diseased tissue that is unresponsive to pressure changes. Healthy units can account for as few as 20% to 30% of total units (194) and can be viewed as a "baby lung" or a "shrunken lung" as described by Gibson and Pride in patients with lung fibrosis (195). Thus, most of the ventilation used during conventional management of these patients may be directed at recruitable and probably more healthy units, resulting in their overdistension. Physicians should bear in mind that protracted regional overinflation can worsen any existing lesion (89, 118).

Terminal airway closure, which may occur at rather high volumes in injured lungs, also has potentially important therapeutic implications. Although this phenomenon has been known for some time, clinicians have been mainly concerned with its consequences for gas exchange. Setting the PEEP above the pressure corresponding to this closing volume was associated with a marked shunt reduction (100–103). Recent experimental studies suggest that an appropriate level of PEEP may prevent further damage (28, 29, 31) by stabilizing terminal units. Using computed tomographic (CT) scan imaging, Gattinoni and colleagues showed that PEEP markedly reduced the fraction of the lung undergoing tidal reopening and collapse during mechanical ventilation of patients with the ARDS (196).

If both high- and low-volume lung injury concepts are clinically relevant, the logical inference is that mechanical ventilation of acutely injured lungs should be placed on the linear portion of the pressure–volume curve (197), above the lower inflection point but below the upper inflection (or "deflection" point) (Figure 20), which may reflect overstretching of the open lung as recently exemplified in a CT scan study by Dambrosio and coworkers (198). This linear portion may be very short. In such case, a V_T that would not be deleterious in normal lungs may lead to excessive end-inspiratory volume when the PEEP is set high enough to be above the lower inflection point. In fact, Muscedere and colleagues found occasional air leaks when they ventilated surfactant-deficient lungs with these settings (31). The only way to avoid both low- and high-volume lung injury therefore seems to be to set the PEEP level above the inflection point and to markedly reduce V_T to minimize any risk of overinflation.

It is beyond the scope of the present report to discuss extensively the relative merits and risks of current mechanical ventilation modalities during acute lung injury in humans. Nevertheless, most currently used strategies emphasize the importance of precisely controlling end-expiratory lung volume and limiting end-inspiratory lung volume (12, 17, 18, 192, 199). This is the case in both pediatric and adult practice. HFO ventilation is very frequently used in hyaline membrane disease of neonates to avoid end-inspiratory lung overstretching (by greatly reducing the V_T), although it has not been clearly shown to be better than conventional mechanical ventilation in terms of morbidity and mortality (200, 201). Recruitment of the lung by a sigh maneuver (14) would also tend to limit the risk of low-volume lung injury. Failure to recruit the lung may result in overdistention of the remaining open alveoli. This

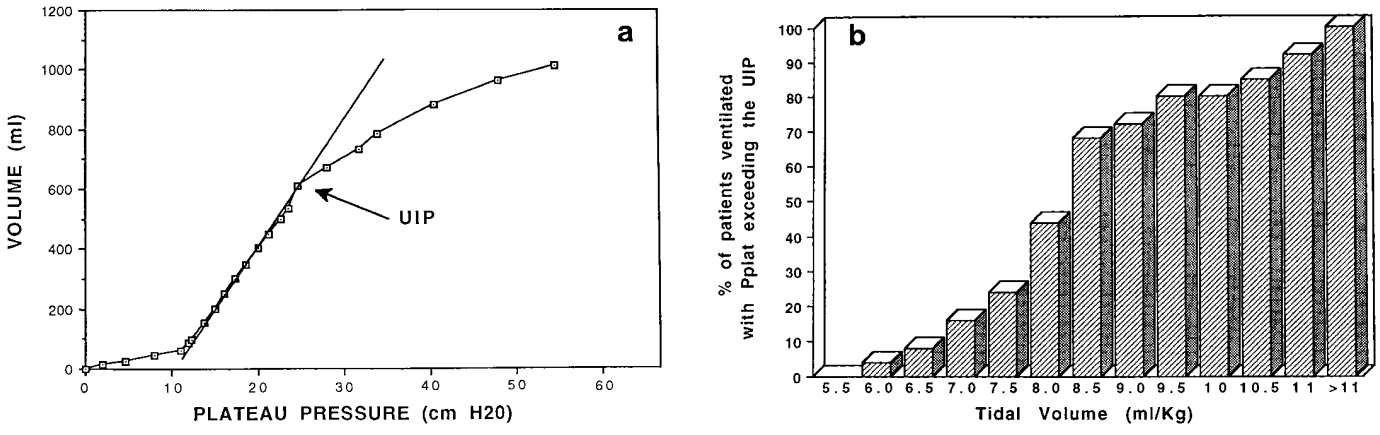

Figure 20. Importance of precise titration of V_T during the mechanical ventilation of ARDS patients with PEEP. (*a*) Pressure–volume curve of the respiratory system in a patient with ARDS. Note the lower inflection point at the bottom of the curve (the curve starts at the level of intrinsic PEEP [PEEPi] measured in this patient). The upper inflection point (UIP) (or "deflection" point) is the first point which departs from linearity. (*b*) Percentage of patients with ARDS whose end-inspiratory plateau pressure exceeded the UIP as a function of V_T during ventilation with PEEP set at the lower inflection point. To keep ventilation in the linear part of the pressure–volume curve, between the lower and upper inflection points, in all patients required V_T reduction to 5.5 ml/kg. Reproduced from Roupie and coworkers (18), with permission.

may be the reason why HFO ventilation has on the whole failed to improve prognosis and was associated with more frequent air leaks during a randomized trial in the treatment of infants with respiratory distress syndrome (200).

HFO ventilation is now seldom used to treat acute lung injury in adults because its effectiveness in terms of reducing morbidity and mortality is not established (110). Nevertheless, in adults too, the objective of "putting the lung at rest" was considered long before experimental studies on ventilator-induced lung injury were available. This was why extracorporeal membrane oxygenation was used, although it did not improve survival over conventional mechanical ventilation (120) and is now only very infrequently used in adults.

Strategies that place ventilation on the linear part of the pressure–volume curve are currently under investigation. They all substantially reduce alveolar ventilation by decreasing V_T, and some of them also reduce respiratory frequency. The resulting CO_2 retention may either be left untreated, as during permissive hypercapnia (15, 202), or offset totally or in part by extracorporeal support using a membrane lung (13, 16) or by washing the dead space with fresh gas delivered into the trachea (159, 203–206). This technique, tracheal gas insufflation, seems interesting because it may increase CO_2 elimination, but it may also increase end-expiratory and end-inspiratory volumes (206). End-expiratory and end-inspiratory pressures also increase when the insufflation of gas is performed during expiration only, because of an auto-PEEP effect (207). Oxygen transport may also be reduced during tracheal gas insufflation (207).

The lungs are kept inflated by a continuous distending pressure interrupted by a few breaths (2 to 4/min) during extracorporeal CO_2 removal. This distending pressure may cause a gradual increase in lung volume. If this volume increase is the result of the recruitment of previously closed lung units, it is likely to be beneficial at least in terms of gas exchange, and will probably not cause additional lung damage, as recently demonstrated by Brunet and colleagues (16). They showed that extracorporeal CO_2 removal lowered arterial P_{CO_2}, despite a significant reduction of V_T. Mean airway pressure decreased in spite of an increase in PEEP, and the number of patients in whom an upper deflection point was found on the pressure–volume curve was significantly reduced, suggesting a decreased risk of lung overstretching. Arterial P_{O_2} increased, the probable consequence of better lung recruitment. Despite these interesting results, this technique was not associated with improved survival during a single-center randomized study (208). The results of large scale multicenter studies are needed before drawing definite conclusions.

Because of the uncertainty that extracorporeal CO_2 removal reduces mortality and the serious problems that may accompany this very invasive technique, it has been suggested that the hypercapnia due to V_T reduction should be accepted (15), as the consequences of progressive respiratory acidosis are probably less serious than the risk linked to overinflation. The potential benefits and hazards of permissive hypercapnia have been recently reviewed in this journal (202). The goal of such a technique is to keep the V_T within certain limits to avoid ventilating injured lungs at low or high volume. However, the difficulty of finding an acceptable pressure range for the V_T was confirmed during the ventilation of patients suffering from ARDS by Roupie and coworkers (18). They showed that ventilation with a PEEP set at the lower inflection point (10 cm H_2O as a mean) and a V_T of only 10 ml/kg took place near total lung capacity in most patients, as shown on the pressure–volume curve by the presence of an upper inflection point within the tidal ventilation. Indeed, the inspiratory plateau pressure (mean value: 31 cm H_2O) was above the pressure at which the upper inflection point was found (mean value: 24 cm H_2O) in 20 of 25 (80%) of these patients. To keep ventilation in the linear part of the pressure–volume curve, between the lower and upper inflection points, in all patients required the V_T to be reduced to 5.5 ml/kg (Figure 19), producing an increase in arterial P_{CO_2} from 44 to 77 mm Hg (18). Similarly, Ranieri and coworkers (209) showed that a PEEP (10 cm H_2O) that resulted in overinflation during "normal" V_T ventilation (10 to 15 ml/kg) of ARDS patients resulted in lung recruitment when the V_T was markedly reduced (5 to 8 ml/kg).

There have been many reports on the effect of reducing V_T. A reduction from 14 to 11 ml/kg BW was found to improve oxygen delivery in ARDS patients ventilated with a 15 cm H_2O PEEP because of better hemodynamics and increased lung compliance (210). An even greater reduction in V_T (from 11 to 8 ml/kg BW [211], and from 12 to 6 ml/kg BW [212]) proved to be safe in these patients: this was associated with little (212) or no (211) change in arterial P_{aO_2} and with increased oxygen delivery (211). A marked reduction of inspiratory airway pressure is needed in order to decrease lung stretch during mechanical ventilation. As exemplified by the above study of Roupie and colleagues (18), setting the plateau pressure to a predetermined level is no guarantee against lung overinflation. This may explain the recent conflicting reports on mortality reduction with pressure–volume limiting strategies during ARDS. Amato and colleagues (17) randomly allocated patients to ventilation with a PEEP level above the inflection point and permissive hypercapnia, or to conventional ventilation (lower PEEP and higher V_T). The lung mechanical properties and gas exchange of the high PEEP–hypercapnia group were markedly improved, but the number of patients was too small to demonstrate whether this strategy resulted in better mortality rates than conventional ventilation. Another preliminary study by the same investigators reported decreased mortality in patients ventilated with permissive hypercapnia (213). In contrast, preliminary reports from three recent randomized trials of reduced V_T by limiting end-inspiratory airway pressure to a predetermined fixed value during ARDS (214, 215), or situations known to predispose patients to ARDS (216), showed no reduction in the mortality rate. These studies have not been published yet, so that it is difficult to account for the difference in outcome. Nevertheless, two main differences in protocol may explain why one study (213) reported improved mortality, whereas the others did not (214–216). First, there was a greater V_T reduction in this study, to below 6 ml/kg, whereas it was 7 ml/kg or more in the others. It is conceivable that the difference of V_T between "conventional" and "reduced V_T" ventilation was not sufficient to affect outcome. Second, in addition to reducing the V_T, Amato and coworkers (213) used a precise titration of PEEP (set above the inflection point) for patients whose V_T was reduced, whereas the other studies did not tailor the PEEP (214–216).

Another way to limit VILI during mechanical ventilation of heterogeneous lungs may be to try to restore more uniform mechanical properties by, for example, surfactant replacement therapy. This approach has clearly been beneficial in neonates with respiratory distress syndrome (217), but the results in adults have been less encouraging (140, 218), with the exception of a recent preliminary study (219). Partial liquid ventilation with perfluorocarbons has recently emerged as yet another way of improving lung mechanical and gas exchanging properties (220–222). Partial liquid ventilation improves ventilator-induced lung injury in rats (119), but it is premature to say whether it will prove beneficial in clinical practice (223,

224). It is beyond the scope of this review to discuss the merits and indications of these therapies.

Finally, the contribution of VILI to the genesis of the multiple organ dysfunction syndrome that may occur in critically ill mechanically ventilated patients (158) deserves some comment. This possibility was first evoked by Kolobow and colleagues (24, 93), who showed that sheep mechanically ventilated with lung overdistension for prolonged periods had clinical features much like those seen in the syndrome of multiple organ failure. Decompartmentalization of bacteria present in the lung (159) or of locally produced cytokines (111, 155–157) may promote remote organ dysfunction.

The main determinant of volutrauma seems to be the end-inspiratory volume (the overall lung distension), rather than the VT or FRC (which depends on PEEP) (88). Consequently, a consensus has emerged as to the importance of monitoring and limiting inspiratory plateau pressure (which reflects end-inspiratory volume better than does peak pressure) during clinical mechanical ventilation, especially during ARDS (12), despite the present uncertainty about its capacity to reduce mortality. The precise level at which this plateau pressure should be limited is a matter of debate (12, 192, 199), especially in light of recent studies (213–216). A recent Consensus Conference on mechanical ventilation recommended that plateau pressure be maintained below 35 cm H_2O in ARDS patients by reducing VT to as low as 5 ml/kg (12). Nevertheless, prevention of overdistension is difficult to demonstrate. Monitoring the upper inflection point of the pressure–volume curve may be an appropriate method, but it has several potential limitations: it is a time-consuming procedure (which, however, would greatly benefit from the further automation of modern respirators [225]), it is not always very easy to determine whether a deflection point is actually present (16), and, finally, CT scan studies show that some areas of the lung may be recruited when others are overstretched (194), making the appreciation of tissue distention from respiratory mechanics only impractical. The development of a simple tool for determining regional volumes during ventilation would therefore be a major step forward in the search for safer treatment.

The prognosis of acute respiratory distress syndrome seems to have improved over the years for reasons that are yet unclear (226) but may be related in part to the lower VT used in most intensive care units at present. The considerable amount of experimental work on the ventilation of acutely injured lungs that has accumulated over recent years has resulted in profound changes in the clinical practice of mechanical ventilation. Further clinical trials will tell us whether these changes have helped to improve the prognosis of acute lung injury.

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