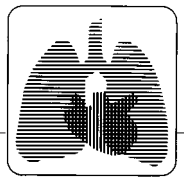

High-Frequency Ventilation for Acute Lung Injury and ARDS*

Jerry A. Krishnan, MD; and Roy G. Brower, MD

In patients with acute lung injury (ALI) and ARDS, conventional mechanical ventilation (CV) may cause additional lung injury from overdistention of the lung during inspiration, repeated opening and closing of small bronchioles and alveoli, or from excessive stress at the margins between aerated and atelectatic lung regions. Increasing evidence suggests that smaller tidal volumes (VTs) and higher end-expiratory lung volumes (EELVs) may be protective from these forms of ventilator-associated lung injury and may improve outcomes from ALI/ARDS. High-frequency ventilation (HFV)-based ventilatory strategies offer two potential advantages over CV for pateints with ALI/ARDS. First, HFV uses very small VTs, allowing higher EELVs with less overdistention than is possible with CV. Second, despite the small VTs, high respiratory rates during HFV allow the maintenance of normal or near-normal $Paco_2$ levels. In this review, the use of HFV as a lung protective strategy for patients with ALI/ARDS is discussed. ***(CHEST 2000; 118:795–807)***

Key words: acute lung injury; ARDS; barotrauma; high-frequency ventilation; high-frequency positive-pressure ventilation; high-frequency jet ventilation; high-frequency oscillation; mechanical ventilation; volutrauma

Abbreviations: ALI = acute lung injury; APACHE = acute physiology and chronic health evaluation; CV = conventional mechanical ventilation; EELV = end-expiratory lung volume; EILV = end-inspiratory lung volume; *f* = respiratory rate; FIO_2 = fraction of inspired oxygen; HFJV = high-frequency jet ventilation; HFO = high-frequency oscillation; HFO-Hi = high-frequency oscillation with high end-expiratory lung volume; HFO-Lo = high-frequency oscillation with low end-expiratory lung volume; HFPPV = high-frequency positive-pressure ventilation; HFPV = high-frequency percussive ventilation; HFV = high-frequency ventilation; I/E = inspiratory/expiratory; MAP = mean airway pressure; NHLBI = National Heart, Lung, and Blood Institute; NIH = National Institutes of Health; PEEP = positive end-expiratory pressure; PFLEX = midpoint of the portion of the pressure-volume curve with increasing slope; PIE = pulmonary interstitial emphysema; RDS = respiratory distress syndrome; UHFV = ultra high-frequency ventilation; VALI = ventilator-associated lung injury; VT = tidal volume

Mechanical ventilation is the cornerstone of supportive care for acute respiratory failure. In most patients, adequate gas exchange can be ensured while more specific treatments are administered and natural healing processes occur. Conventional approaches to mechanical ventilation utilize tidal volumes (VTs) that are approximately 75 to 150% of the volumes that patients typically achieve during spontaneous ventilation.[1] While conventional ventilation (CV) usually provides adequate gas exchange, it is sometimes associated with high airway pressures, circulatory depression, and pulmonary air leaks. These adverse effects stimulated the development of high-frequency ventilation (HFV). There was great enthusiasm for HFV during its early development in the 1970s and 1980s. Scores of studies in animals and humans were conducted to understand the physiology of gas exchange[2–5] and its effects on circulation and other systems[6,7] and to improve the techniques of HFV. However, the initial enthusiasm for HFV waned as clinical studies failed to demonstrate important advantages over CV.[8–10]

There is now renewed interest in HFV because of increasing evidence that (1) CV may contribute to lung injury in patients with acute lung injury (ALI) and ARDS,[11] and (2) modifications of mechanical

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The authors have no financial interest in the subject discussed in this article.
Manuscript received January 24, 2000; accepted January 25, 2000.
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Table 1—*Selected Features of CV and HFV*

Ventilator Type	*f*, Breaths/min	Inspiration	Expiration
CV	2– approximately 40	Active	Passive
HFPPV	approximately 60–100	Active	Passive
HFJV	approximately 100–200	Active	Passive
HFO	Up to approximately 2,400	Active	Active

ventilation techniques may prevent or reduce lung injury and improve clinical outcomes in these patients.[12–14] The primary objective of this review is to discuss the potential role of HFV for achieving adequate gas exchange while protecting the lung against further injury in patients with ALI/ARDS. The review begins with an overview of HFV techniques and a summary of potential mechanisms of gas transport. The rationale for the use of HFV-based lung protective strategies in the management of patients with ALI/ARDS will be explained. The results of animal and human studies evaluating HFV for ALI/ARDS will be discussed.

HFV

HFV is a mode of mechanical ventilation that uses rapid respiratory rates (respiratory rate [*f*] more than four times the normal rate) and small VTs. Although HFV VTs are often smaller than traditional estimates of both anatomic and physiologic dead space, adequate oxygenation and ventilation usually can be achieved.[15] There are numerous variations of HFV. These may be broadly classified as high-frequency positive pressure ventilation (HFPPV), high-frequency jet ventilation (HFJV), and high-frequency oscillation (HFO). These classes of HFV are compared in Table 1 and are briefly discussed herein.

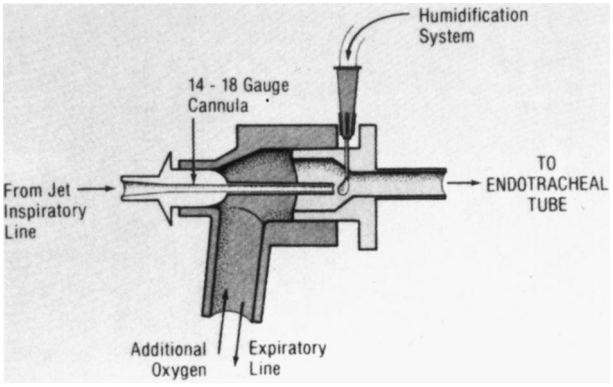

FIGURE 1. Section of HFJV. Note the expiratory conduit through which additional gas is entrained during inspiration. Reprinted with permission from Carlon et al.[20]

More detailed descriptions can be found in other reviews.[15,16]

HFPPV was introduced by Oberg and Sjöstrand[17] in 1969 to eliminate the effect of respiratory variations in thoracic volume and pressure on carotid sinus reflexes.[16] HFPPV delivers small VTs (approximately 3 to 4 mL/kg) of conditioned gas at high flow rates (175 to 250 L/min) and frequency (*f*, 60 to 100 breaths/min). The precise VT is difficult to measure during HFPPV because some gas flows through the expiratory conduit during inspiration. Expiration is passive and depends on lung and chest wall elastic recoil. Thus, with high *f*, there is a risk of gas trapping with overdistention of some lung regions and adverse circulatory effects. HFPPV was used primarily in situations requiring minimal upper airway movement, such as laryngoscopy, bronchoscopy, and laryngeal surgery.[18]

Sanders[19] introduced HFJV in 1967 to facilitate gas exchange during rigid bronchoscopy. In HFJV, gas under high pressure (15 to 50 lb per square inch) is introduced through a small-bore cannula or aperture (14 to 18 gauge) into the upper or middle portion of the endotracheal tube (Fig 1).[20] Pneumatic, fluid, or solenoid valves control the intermittent delivery of the gas jets. Aerosolized saline solution in the inspiratory circuit is used to humidify the inspired air. Some additional gas is entrained during inspiration from a side port in the circuit. This form of HFV generally delivers a VT of 2 to 5 mL/kg at a *f* of 100 to 200 breaths/min. The jet pressure (which determines the velocity of air jets) and the duration of the inspiratory jet (and, thus, the inspiratory/expiratory ratio [I/E]) are controlled by the operator. Together, the jet velocity and duration determine the volume of entrained gas. Thus, the VT is directly proportional to the jet pressure and I/E. Because the volume of entrained air is not operator-controlled, it is difficult to manipulate with precision the VTs delivered during HFJV. The jet pressure and the duration of the inspiratory jet are adjusted empirically to achieve adequate ventilation. During HFJV, high inspiratory airflow rates and the decompression of jet gas prevent optimal humidification and warming of inspired air, increasing the risk of airway obstruction with desiccated secretions and epithelial debris.[15,21] As with HFPPV, expiration is passive. Thus, HFJV may cause air trapping.

Lunkenheimer et al[22] introduced HFO in 1972. HFO uses reciprocating pumps or diaphragms. Thus, in contrast to HFPPV and HFJV, both expiration and inspiration are active processes during HFO. HFO VTs are approximately 1 to 3 mL/kg at *f*s up to 2,400 breaths/min. The operator sets the *f*, the I/E (typically approximately 1:2), driving pressure, and mean airway pressure (MAP). Driving pressure (also

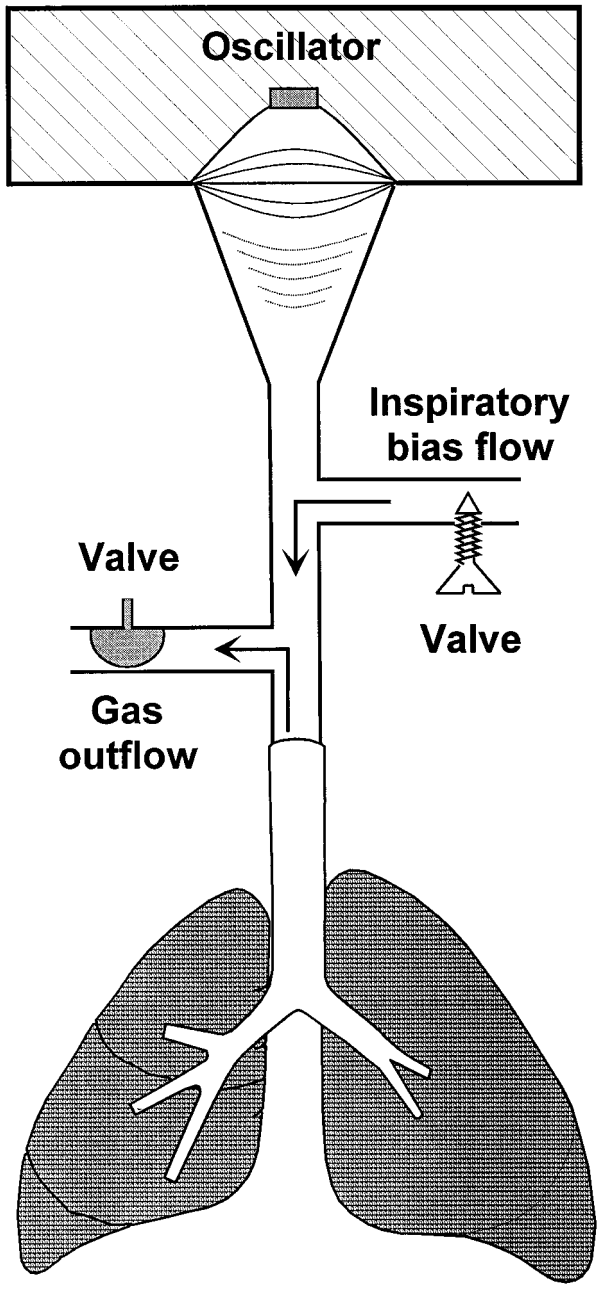

FIGURE 2. Schematic of HFO. An oscillating diaphragm or pump creates sinusoidal inspiratory and expiratory air flows. Changes in inspiratory bias flow are used to adjust the MAP.

known as *power*) is determined by the displacement of the reciprocating pumps or diaphragms. The oscillatory VTs generated during HFO are directly related to driving pressures. In contrast, VTs are inversely related to *f*, since shorter inspiratory times reduce the duration of bulk flow of air into the tracheobronchial tree (see the "Gas Transport During HFV" section). The inspiratory bias flow of air into the airway circuit is adjusted to achieve the desired MAP, an important determinant of oxygenation (Fig 2). There is no gas entrainment or decompression of gas jets in the airway, allowing better humidification and warming of inspired air. This lowers the risks of airway obstruction from desiccated airway secretions. In addition, active expiration permits better control of lung volumes than with HFPPV and HFJV, decreasing the risk of air trapping, overdistention of airspaces, and circulatory depression. Lower I/Es (1:2 or 1:3) reduce the risk of air trapping. Periodic assessments of BP and lung volume on chest roentgenograms are used to identify air trapping. Peak inspiratory airway pressure does not accurately reflect lung volume or air trapping because inspiratory airway pressure is substantially greater than alveolar pressure.

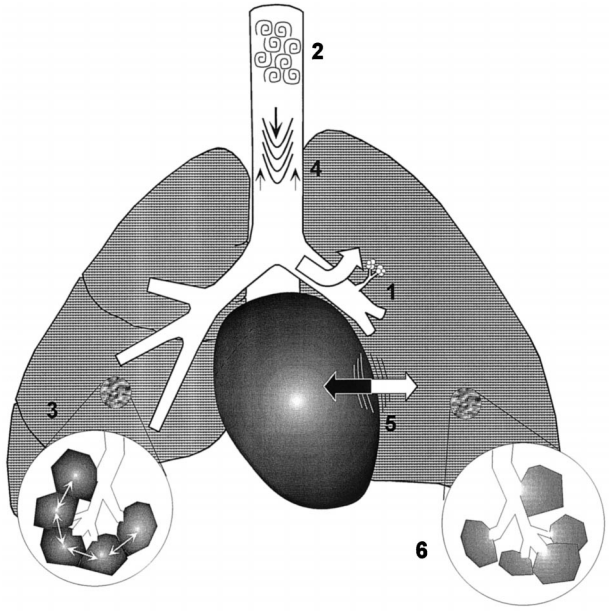

FIGURE 3. Proposed mechanisms of gas transport during HFV. 1 = direct bulk flow; 2 = longitudinal (Taylor) dispersion; 3 = pendeluft 4 = asymmetric velocity profiles; 5 = cardiogenic mixing; 6 = molecular diffusion. Adapted with permission from Chang.[23]

GAS TRANSPORT DURING HFV

Research directed toward understanding the mechanisms of gas exchange during HFV have led to many insights into pulmonary physiology. Several mechanisms of gas mixing may contribute to gas transport during HFV. These are reviewed briefly here and in Figure 3.[23] More detailed descriptions of the physiology of gas exchange with HFV are presented elsewhere.[5,23]

Direct Bulk Flow

Some alveoli situated in the proximal tracheobronchial tree receive a direct flow of inspired air. This leads to gas exchange by traditional mechanisms of convective or *bulk* flow.

Longitudinal (Taylor) Dispersion

Turbulent eddies and secondary swirling motions occur when convective flow is superimposed on diffusion. Some fresh gas may mix with gas from alveoli, increasing the amount of gas exchange that would occur from simple bulk flow.

Pendeluft

In healthy and, more so, in diseased lungs, the mechanics of air flow vary among lung regions and units within regions. Variation in regional airway resistance and compliance cause some regions to fill and empty more rapidly than others. Some gas may flow between regions if these characteristics vary among regions that are in close proximity.

Asymmetric Velocity Profiles

The velocity profile of air moving through an airway under laminar flow conditions is parabolic. Air closest to the tracheobronchial wall has a lower velocity than air in the center of the airway lumen. This parabolic velocity profile is usually more pronounced during the inspiratory phase of respiration because of differences in flow rates. With repeated respiratory cycles, gas in the center of the airway lumen advances further into the lung while gas on the margin (close to the airway wall) moves out toward the mouth.

Cardiogenic Mixing

Mechanical agitation from the contracting heart contributes to gas mixing, especially in peripheral lung units in close proximity to the heart.

Molecular Diffusion

As in other modes of ventilation, this mechanism may play an important role in mixing of air in the smallest bronchioles and alveoli, near the alveolocapillary membranes.

ALI/ARDS

The next sections review the following topics: (1) pertinent aspects of ALI/ARDS pathophysiology; (2) evidence that CV may perpetuate or exacerbate lung injury; and (3) experience with CV-based and HFV-based strategies to improve outcomes in these conditions.

ALI/ARDS occurs when conditions such as pneumonia, sepsis, or severe trauma lead to acute inflammation in the pulmonary parenchyma,[24,25] increased pulmonary vascular permeability,[26] and extravasation of proteinaceous fluid into the pulmonary interstitium and alveoli.[27,28] Surfactant production is reduced by injury to type II pneumocytes, and existing surfactant is inactivated by plasma proteins that leak into the airspaces.[29,30] The loss of surfactant function increases surface tension at air-fluid interfaces and leads to the microatelectasis of alveoli and other small airways.[31]

Although chest radiographs of patients with ALI/ARDS are frequently interpreted to show diffuse infiltrates, CT images, histologic sections, and physiologic studies indicate that the lung injury in these conditions is not uniform.[32,33] Some regions are severely affected by acute inflammation, airspace filling, and atelectasis, and others appear to be completely spared.

Patients with ALI/ARDS frequently develop acute respiratory failure, with worsening arterial oxygenation due to intrapulmonary shunt and ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch. Physiologic dead space typically is also elevated,[34–36] which increases the minute ventilation required to maintain normal arterial $Paco_2$ and pH. Mechanical ventilation is frequently necessary to maintain gas exchange and to allow more time for specific treatments and natural healing processes. Because lung injury is patchy, ventilation is distributed unevenly. Lung regions and units with worse injury have reduced compliance. V_Ts are distributed to the less injured, more compliant regions. Numerous studies have shown that mechanical forces during CV cause or worsen lung injury under these circumstances. This potential complication is known as ventilator-associated lung injury (VALI). Moreover, various proinflammatory mediators may be released when lungs are subjected to injurious mechanical forces.[13,37–39] These mediators may contribute to further injury to the lung and other organs.[13,37] Thus, traditional approaches to mechanical ventilation in patients with ALI/ARDS may perpetuate lung injury and contribute to the development of multiorgan dysfunction syndrome.[11,13]

Mechanisms of VALI in ALI/ARDS

VALI may occur as a result of several mechanisms related to the uneven distribution of ventilation.[40–42] First, ventilation of lung regions with higher compliance may be injured by excessive regional end-inspiratory lung volumes (EILVs). Second, injury may occur in small bronchioles when they snap open during inspiration and close during expiration. Third, pulmonary parenchyma at the margins between atelectatic and aerated units may be injured by excessive stress from the interdependent connections

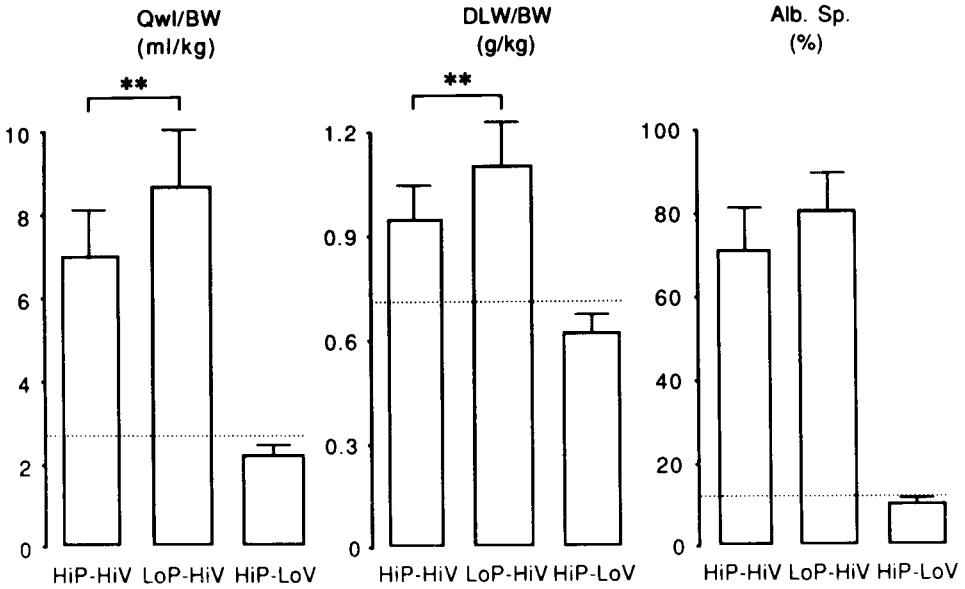

FIGURE 4. Measures of lung injury according to lung volumes and airway pressures. Extravascular lung water (Qwl), dry lung weight (DLW), and albumin space (Alb Sp) adjusted for body weight (BW) in rats ventilated for 20 min with high airway pressures and high VTs (HiP-HiV) (using a peak airway pressure of 45 cm H_2O and a VT of approximately 40 mL/kg), low pressure and high volume (LoP-HiV) (using negative inspiratory pressure from iron lung to achieve a VT of approximately 44 mL/kg), and high pressure and low volume (HiP-LoV) (using thoracoabdominal strapping to achieve a peak airway pressure of 45 cm H_2O and a VT of approximately 19 mL/kg). Higher Qwl, DLW, and Alb Sp represent measures of greater lung injury. Horizontal dotted lines represent the upper 95% confidence limit for control values. Rats ventilated with HiP-HiV and LoP-HiV, but not HiP-LoV, had significantly more lung injury than control rats ($p < 0.01$). ** = significant difference between the groups indicated ($p < 0.01$). Reproduced with permission from Dreyfuss et al.[45]

between adjacent units. These last two mechanisms are frequently described with the term *shear forces* and may be important mechanisms of lung injury when ventilation occurs with relatively low end-expiratory lung volumes (EELVs) in patients with ALI/ARDS.

Injury From Excessive EILVs

The lungs of patients with ALI/ARDS are susceptible to excessive regional EILV and overdistention injury because VTs are distributed primarily to the relatively small portions of lung that are unaffected by the initial injury. Many studies in experimental animals have demonstrated acute inflammation, increased vascular permeability,[27,28] intra-alveolar hemorrhage,[28] radiographic infiltrates,[43] and hypoxemia[28,43] resulting from overdistention of the healthy lung. Additional studies in animals with experimental ALI have shown worsening of lung injury or delayed resolution of edema when there was excessive EILV.[11,44]

High inspiratory airway pressures (peak and plateau) are commonly observed and frequently implicated as causes of VALI. However, excessive lung stretch, rather than pressure, is more likely to be the injurious force (Fig 4).[45,46] Elevated airway pressures are recognized as markers of excessive stretch, but high airway pressures without excessive lung volumes are not injurious to the lung.[41] Thus, there is increasing use of the term *volutrauma* to refer to the stretch-induced injury of excessive inspiratory gas volume.[11,46]

Injury From Ventilation at Low EELVs

Positive end-expiratory pressure (PEEP) has lung protective effects during mechanical ventilation in isolated lungs,[40] and in intact[41,44,47,48] and open-chest animals.[49] In intact healthy rats, edema and hemorrhage from ventilation with excessive lung volumes were substantially reduced when PEEP was used (Fig 5).[48] In a dog lung injury model,[44] lung injury (assessed from lung wet weight to body weight ratio and venous admixture) was caused by ventilation with large VT and low PEEP. This injury was reduced in animals ventilated with smaller VTs and higher PEEPs despite similar EILVs. The effect of end-expiratory atelectasis on lung injury was evaluated in a rabbit surfactant-deficient model.[50] Rabbits ventilated with negative end-expiratory pressure demonstrated greater alveolar capillary permeability,

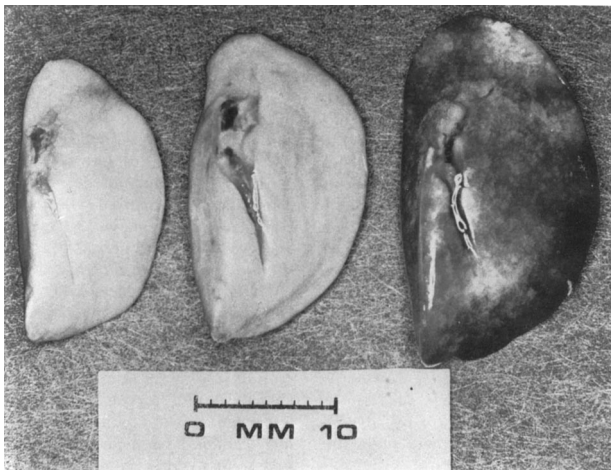

FIGURE 5. Comparison of rat lungs after ventilation at various airway pressures. Peak airway pressures and PEEPs of 14 cm H_2O and 0 cm H_2O, respectively (strategy A, *left*), 45 cm H_2O and 10 cm H_2O, respectively (strategy B, *middle*), or 45 cm H_2O and 0 cm H_2O, respectively (strategy C, *right*) were used during the 60-min experimental period (unless death occurred earlier). On gross examination, the perivascular groove was distended after strategy B, and the lung appeared dark and congested after strategy C. There were no histopathologic changes in nonventilated control lungs and lungs ventilated with strategy A. After strategy B, perivascular edema was slightly increased. After strategy C, there was marked edema and hemorrhage in the perivascular and alveolar spaces, and all rats died after 13 to 35 min. Reproduced with permission from Webb and Tierney.[48]

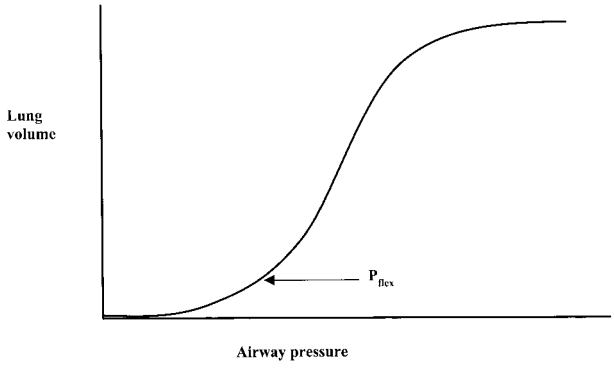

FIGURE 6. Respiratory system pressure-volume curve.

reduced lung compliance, and worse gas exchange than rabbits ventilated with PEEP.

These and other studies provide convincing evidence that PEEP has lung protective effects during mechanical ventilation. However, PEEP also can contribute to lung injury by raising EILV unless VT is simultaneously reduced. Moreover, PEEP may cause circulatory depression from increased pulmonary vascular resistance and decreased venous return. Thus, determining the optimal level of PEEP in individual patients represents a difficult and tenuous balance between potential lung protective effects and deleterious effects on the lung and other systems.

Some investigators have used static or quasi-static pressure-volume curves of the respiratory system to explain the effects of ventilation at low EELV, to predict the effects of ventilation with higher PEEPs and EELVs, and to identify the best PEEP to apply during CV to achieve lung protection.[12,40,51,52] The slope of the pressure-volume relationship (Fig 6) represents compliance of the respiratory system. Compliance in the lower portion of the curve increases as airway pressure and volume rise, representing gradual recruitment of atelectatic portions of the lung. This interpretation is supported by improved arterial oxygenation[53] and CT evidence of increased lung aeration in ARDS patients.[54] The midpoint of the portion of the pressure-volume curve with increasing slope is frequently labeled "PFLEX" and may represent the inspiratory airway pressure and volume where many lung units are open.[55] The mid-portion of the pressure-volume curve appears to be virtually rectilinear. This region of approximately constant compliance has been interpreted to represent a range of airway pressures and lung volumes in which little or no further recruitment occurs.

Some workers have advocated setting PEEP to approximately PFLEX plus 2 cm H_2O to prevent the closure of unstable lung units during expiration and, thus, to prevent injurious shear forces from ventilation with insufficient EELV.[12] This recommendation is supported by the results of studies suggesting that CV with PEEP that is less than PFLEX may cause VALI. In a nonperfused rat model of lung injury, for example, the effects of ventilation with PEEP that is below and above PFLEX on lung injury were compared.[40] Lung compliance, bronchiolar epithelial necrosis and sloughing, and hyaline membranes were significantly more common in the lungs ventilated with PEEP less than PFLEX than in lungs ventilated with PEEP more than PFLEX and in control (nonventilated) lungs. There was no significant difference in these measures of VALI between the latter two groups. In surfactant-deficient rabbits, mechanical ventilation with PEEP equal to PFLEX minus 5 cm H_2O was compared to ventilation with PEEP equal to PFLEX.[51] Ventilation with PEEP less than PFLEX was associated with greater hypoxemia and more hyaline membrane formation than ventilation with PEEP equal to PFLEX.

CV-Based Lung Protective Strategies

CV strategies designed to protect the lung from VALI have been tested in several clinical trials.

Studies With Reduced EILV

In two case series of patients with severe ARDS (a total of approximately 100 patients), ventilation with small VTs (reduced EILVs) was associated with mortality rates that were substantially lower than rates predicted from the patients' acute physiology and chronic health evaluation (APACHE) II scores.[56,57] However, severe respiratory acidosis occurred in some patients treated with small VTs, and previous animal studies have suggested that respiratory acidosis could cause circulatory depression.[58–60] Moreover, respiratory acidosis worsens dyspnea and agitation, which could increase requirements for sedatives and, in some patients, neuromuscular blockade. Because patients treated with traditional CV strategies were not included in these studies, it was not clear that the beneficial effects of reduced EILV outweighed the potential disadvantages.

Three modestly sized randomized clinical trials failed to show beneficial effects of CV-based small VT ventilation in comparison with more traditional VT strategies in patients with or at risk for ARDS.[61–63] In contrast, a large multicenter trial with $>$ 861 patients with ALI/ARDS conducted by the National Institutes of Health (NIH)/National Heart, Lung, and Blood Institute (NHLBI)-sponsored ARDS Network found substantial improvements in clinical outcomes in the small VT group.[14] The mortality rate prior to discharge home with unassisted breathing was significantly reduced (31% vs 40%, respectively; $p < 0.01$) among patients randomized to the small VT strategy.[14] Possible reasons for the different results in this trial in comparison to the previous three studies include greater separation in VT between treatment groups, greater statistical power to detect differences in outcomes (larger sample size), and more active management of respiratory acidosis.

Studies With Reduced EILV and Increased EELV

A clinical trial in 53 patients with severe ARDS compared a traditional CV approach with an approach designed to protect the lung from VALI resulting from both excessive EILV and inadequate EELV.[12] In the lung-protection group, pressure-limited modes were used with VTs $\leq$ 6 mL/kg and peak inspiratory pressures $<$ 40 cm H_20 to reduce EILV. Increased EELV was achieved, raising PEEP to PFLEX plus 2 cm H_20 during the initial stages of lung injury. Frequent recruitment maneuvers were introduced to further increase EELV, and additional measures were taken to avoid undesirable collapse or derecruitment of some lung regions. The lung protection approach was associated with an improved 28-day survival rate and weaning rate. There was also an encouraging trend toward reduced in-hospital mortality rate. However, this was a relatively small trial, and the mortality rate in the traditional CV group (71%) was higher than those of several previous studies.[64–67] Also, it is not clear from the results of this study which of the lung protection measures improved outcomes. If higher PEEPs contributed to the improved outcomes in the lung-protection group, it is not clear that PFLEX plus 2 cm H_2O was the best PEEP. Perhaps there would be even further benefit with higher PEEPs in achieving even greater EELV or with lower PEEPs to protect against adverse effects from excessive EILV.

Summary: Lung Protective Modes of CV

Taken together, the body of experimental evidence from animals as well as humans strongly suggests that a lung protective strategy with smaller EILV and higher EELV will reduce VALI and improve outcomes in patients with ALI/ARDS. However, CV-based lung protective strategies have several limitations. First, safe limits for EILV have not been clearly defined.[68] Both peak and plateau inspiratory pressures are influenced greatly by chest wall as well as lung mechanics. The amount of stretch in the lungs of patients with normal chest wall compliance may be greater than in the lungs of patients with reduced chest wall compliance at any level of peak or plateau airway pressure. No firm recommendations have been established to adjust airway pressure thresholds for patients with different chest wall characteristics. Measurement of esophageal pressures will allow estimations of pleural pressures, which can be used to monitor and limit peak transpulmonary pressure. When this technique is used rigorously, it provides the opportunity to eliminate the influence of chest wall compliance on airway pressures and to focus specifically on distending forces in the lung. While this approach is logical and based on sound physiologic principles, its use as a clinical tool has not been widely accepted and safe limits for transpulmonary pressures have not been defined. It is likely that stretch and lung injury gradually rise as airway pressures and volumes rise and that mildly injurious stretching occurs in some regions of the lung at relatively low lung volumes and pressures. More information is needed to define the relationships of lung volumes and airway pressures on stretch injury in individual patients and to balance the potential benefits of marginal reductions in stretch with potential problems associated with decreased alveolar ventilation. Without this information, clinicians using CV in ALI/ARDS patients may feel compelled to use smaller and smaller VTs to achieve potential but uncertain increments in lung

protection at the risk of severe hypercapnia, respiratory acidosis, and hemodynamic compromise.

Second, the optimal EELV for individual patients has not been defined. The use of the PFLEX is problematic for several reasons. Static or quasi-static pressure-volume curves do not depict the relationship of lung volume to airway pressure during tidal ventilation.[69,70] In addition, PFLEX frequently cannot be clearly identified on static pressure-volume curves in patients with ALI/ARDS.[71,72] Moreover, when a PFLEX can be identified, it often reflects characteristics of the chest wall rather than the lung.[73] Also, alveolar recruitment continues as airway pressure and lung volume rise above their levels at PFLEX.[74,75] Thus, it is not at all clear that maximal lung protection is achieved at PFLEX, at PFLEX plus 2 cm H_2O, or at any value above or below PFLEX. Finally, increasing EELV (with higher PEEPs), especially when it is used in combination with lower EILVs (smaller VTs) during CV, will cause hypoventilation and may lead to respiratory acidosis,[56,57] dyspnea, circulatory depression,[58–60] increased cerebral blood flow, and risk for intracranial hypertension,[76,77] and it could increase the requirements for heavy sedation and neuromuscular blockade. Prolonged neuromuscular blockade, especially with concomitant corticosteroid use, may cause neurologic complications, including myopathy and neuropathy.[78] Clinicians must consider these risks when using higher PEEPs as part of a CV-based strategy to reduce lung injury.

Rationale for HFV-Based Lung Protective Strategies

HFV is an attractive mode of ventilation in patients with ALI/ARDS because of the following advantages over CV:

1. *HFV uses very small VTs*. This allows the use of higher EELVs to achieve greater levels of lung recruitment while avoiding injury from excessive EILV.
2. *Respiratory rates with HFV are much higher than with CV*. This allows the maintenance of normal or near-normal $PaCO_2$ levels, even with very small VTs.

Because of these advantages, some investigators have advocated the use of HFV in patients with ALI/ARDS.[15,79] The following sections review the results of studies of HFV in animal models of lung injury, pediatric patients with acute respiratory failure, and adults with ALI/ARDS.

HFV for ALI and ARDS

Animal Studies

Some studies in premature primate models of surfactant deficiency failed to show consistent beneficial effects during HFV.[80–84] In contrast, several studies found that HFV was superior to CV when HFV was used as part of a strategy to achieve higher EELV.[47,85–88] In a rabbit model of surfactant deficiency following saline solution lung lavage, 5 to 7 h of ventilation with HFJV after a volume-recruitment maneuver (sustained inflation to 30 cm H_2O for 15 s) resulted in lower peak airway pressures and MAPs and fewer hyaline membranes than CV.[85] In a separate study, adult rabbits after lung lavage were randomized to a 7-h period of ventilation with HFO with high EELV (HFO-Hi) or with HFO with low EELV (HFO-Lo), to CV, or to a control group in which animals were killed after the lavage.[47] All rabbits randomized to CV died (three of five rabbits had pneumothoraces), whereas none died in the HFO-Hi or HFO-Lo groups. Total respiratory system compliance at the end of the experimental period was highest in the HFO-Hi group, lower in the HFO-Lo group, and lowest in the CV group. Microscopic examination revealed substantially more hyaline membrane formation and bronchiolar epithelial injury in the CV group, less in the HFO-Lo group, and little to none in the HFO-Hi group. Animals randomized to the HFO-Hi group had significantly higher PaO_2 levels than those in either the HFO-Lo or CV groups. Thus, HFO with higher lung volumes was associated with superior lung mechanics, less lung injury, and improved oxygenation than was HFO-Lo or CV. In another surfactant-deficient rabbit model, the administration of exogenous surfactant followed by ventilation with HFO and high EELVs was associated with better preservation of surfactant function when compared with CV.[86]

Other studies have demonstrated reduced lung inflammation with HFO. In a surfactant-deficient rabbit model, the effects of HFO and CV at a similar MAP and fraction of inspired oxygen (FIO_2) on lung injury were compared.[87] Rabbits in the HFO group had fewer granulocytes and lower levels of platelet-activating factor and thromboxane B_2 in BAL fluid. In a rabbit surfactant-deficient ALI model, accumulations of lung granulocytes and activation of respiratory bursts in airspaces were greater with CV than with HFO.[88]

In another rabbit lung-lavage study, animals were randomized to HFO (f, 900 breaths/min), HFPPV (f, 120 breaths/min), or HFO combined with CV (HFO with $f = 900$ breaths/min superimposed during the expiratory phase of CV at $f = 40$ breaths/min).[89]

Each of the three study groups received a high EELV strategy with sustained inflations every 20 min and MAP at PFLEX plus 2 cm H_2O. At the end of the 6-h experimental periods, rabbits randomized to HFO had better oxygenation and lung mechanics and less histologic evidence of lung injury than those in the other two groups.

Pediatric Studies

Promising results in surfactant-deficient animal models of lung injury led to studies evaluating HFV for neonatal respiratory distress syndrome (RDS), the most common cause of lung injury in the newborn,[90] which is caused by insufficient surfactant production in immature lungs.[91] Neonates with RDS experience acute respiratory failure and require mechanical ventilatory support until the immature lung can produce enough surfactant to allow adequate respiratory mechanics and gas exchange. In many respects, RDS is physiologically and histologically similar to ALI/ARDS.[90] Although the use of mechanical ventilation is associated with a reduction in mortality due to RDS, morbidity with chronic lung disease (supplemental oxygen requirements and abnormal chest radiographs at approximately 30 days of life) develops in 20 to 60% of preterm infants with RDS.[92]

HFJV and CV were compared in a study of 144 neonates (mean gestational age, approximately 29 weeks) who developed pulmonary interstitial emphysema (PIE; a form of VALI in RDS) after receiving CV.[93] The mean age at the start of the study was approximately 2 days. A greater proportion of neonates randomized to HFJV showed improvement in PIE (61% vs 37%; $p < 0.01$). The incidence of chronic lung disease was lower (but not significantly different) in the HFJV group. Overall, the mortality rate was similar in both groups. To assess the effects of HFV started earlier in the course of RDS, HFJV (with a lung recruitment strategy) was compared to CV in 130 preterm neonates (mean gestational age, approximately 27 weeks) who had not yet developed significant bilateral PIE.[94] The mean age at the start of this study was approximately 8 h. Fewer neonates randomized to HFJV developed chronic lung disease at 36 weeks postconception than those randomized to CV (20.0% vs 40.4%; $p < 0.05$). The survival rates at 36 weeks postconception (HFJV, 84.6%; CV, 80%) and the incidences of chronic lung disease 28 days after birth (HFJV, 67.3%; CV, 71.2%) were similar. These findings are difficult to interpret, however, because 29 of 65 of the HFJV neonates were not managed with a high EELV strategy.

Uncontrolled observational studies suggested that HFO could reduce lung injury in low-birth-weight infants[95] and could improve gas exchange in older children[96] with acute respiratory failure. However, these benefits were not confirmed in a large multicenter, randomized, clinical trial of HFO vs CV in 673 preterm infants with acute respiratory failure.[9] Moreover, HFO was associated with a significantly greater incidence of adverse events, including pneumoperitoneum, grade 3 and 4 intracranial hemorrhage, and periventricular leukomalacia. The interpretation of these results is limited because the trial was conducted prior to the era in which exogenous surfactant was routinely used for the treatment of neonatal RDS. Moreover, the trial procedures did not use a strategy to increase EELV with HFO.

Other clinical trials have shown more encouraging results with HFO compared to CV for the treatment of RDS. In a presurfactant era study employing a crossover trial design, 79 neonates with respiratory failure requiring substantial levels of CV support were randomized to HFO or continued CV.[97] Neonates randomized to HFO met predefined treatment failure criteria somewhat less often than neonates randomized to CV (44% vs 60%, respectively; p value was not significant). Among patients meeting failure criteria on the initial ventilator assignment, however, more responded after crossover to HFO than to CV (63% vs 23%, respectively; $p = 0.03$). There were no differences in mortality rates, ventilator days, or other clinical outcomes between the two groups. Neonates in the CV group appeared to be less ill at baseline, and the study was terminated early due to low enrollment. Thus, the results may have reflected confounding due to baseline differences in the treatment groups, and the trial may have been insufficiently powered to detect small differences in clinical outcomes.

A second study evaluated the role of HFO in 83 premature neonates with RDS.[98] Using a crossover study design, 26 neonates were assigned to CV only, 27 were assigned to HFO for 72 h followed by CV (HFO/CV), and 30 were assigned to HFO only. The incidence of chronic lung disease was significantly lower in the HFO-only group than in the CV-only group. However, there were no significant differences in the incidence of other clinical outcomes between treatment groups, including pulmonary air leak, intraventricular hemorrhage, and mortality. In a third trial, 175 neonates with RDS who were < 48 h old were randomized to HFO or CV.[99] The HFO procedures in this trial used higher MAPs to achieve greater levels of lung recruitment. HFO was associated with a similar mortality rate but a reduced incidence of air leak syndrome (48% vs 63%, respectively; $p < 0.05$). In a fourth study, 125 neonates with RDS received exogenous surfactant before randomization to CV or HFO.[100] HFO reduced vaso-

pressor requirements, surfactant dosing requirements, and the incidence of chronic lung disease. This experimental approach was extended to older children (mean age, 2.5 years) who were receiving CV for acute respiratory failure.[101] Children randomized to HFO required less supplemental oxygen support at 30 days compared with children who continued on CV.

Adults Studies

In a series of five patients with acute respiratory failure of diverse etiologies, PaO_2 did not improve with HFJV when similar levels of PEEP and FIO_2 were used in HFJV and CV.[102] Ultra high-frequency ventilation (UHFV), a modified form of HFJV, was evaluated in 90 medical and surgical patients with ARDS.[103] UHFV uses a solenoid valve to achieve jet pulses of gas at rates that are higher than those used with HFJV (*f*, 60 to 1,200 breaths/min). Patients were eligible if their FIO_2 was > 0.7 with a PaO_2 of 65 mm Hg, a peak inspiratory pressure of 65 cm H_2O, or a PEEP of 15 cm H_2O on CV. Oxygenation improved significantly after 24 h of UHFV (arterial to alveolar ratio increase [mean ± SD], 0.14 ± 0.07 to 0.26 ± 0.14; $p < 0.01$). However, oxygenation was compared at different FIO_2 levels during CV and UHFV, thereby limiting the interpretation of these findings.

HFJV was compared to CV in a randomized trial of 309 oncology patients with body weight ≥ 20 kg and respiratory failure requiring mechanical ventilation.[8] Patients were eligible if they developed respiratory failure with bilateral infiltrates and hypoxemia following surgery or sepsis. Both immunocompetent and immunocompromised (*eg*, following bone marrow transplantation) patients were enrolled. There were no significant beneficial effects of HFJV, including mean (± SE) ICU length of stay (CV, 5.2 ± 0.5 days; HFJV, 4.5 ± 0.3 days) and mortality rate (CV, 62%; HFJV, 62%). However, as in the earlier pediatric studies with HFO, no lung recruitment strategy was used in either group. Moreover, the inclusion of patients with dissimilar levels of immune competence and with respiratory failure from causes other than ALI/ARDS may have confounded these results.

In another study, 113 surgical ICU patients at risk for ARDS were randomized to high-frequency percussive ventilation (HFPV) or CV.[10] HFPV is a hybrid of CV and HFV in which high-frequency airway pressure oscillations are superimposed on traditional VTs and rates. Sixty patients (53%) developed ARDS (32 receiving HFPV; 28 receiving CV). Four patients crossed over to the alternate mode of ventilation after failing to meet predefined criteria for improvement in oxygenation within 24 h of study entry. After another 24 h, the ventilatory mode in which patients achieved the best arterial oxygenation was used for the remainder of the study. Thirteen patients were removed from the study due to protocol violations or insufficient data and were not included in subsequent analyses. There were no differences in clinical outcomes (hospital days, length of ICU stay, or ventilator days) between the treatment groups. These findings are not surprising since ventilation with HFPV entails similar overall changes in intrathoracic volume (and, thus, risk of VALI) during tidal breathing as that with CV.

In a 1997 case series, 17 medical and surgical patients (age range, 17 to 83 years) with severe ARDS who had a mean (± SD) APACHE II score of 23 ± 7.5, and who required high FIO_2 levels, high airway pressures, or high PEEPs after various periods of CV ([mean ± SD] 5.1 ± 4.3 days) were placed on HFO.[79] The HFO procedures included volume recruitment maneuvers and were associated with significant improvements in gas exchange without adverse hemodynamic effects. The survival rate was 47% in this high-risk group of patients. These results demonstrate the feasibility of ventilating adults with ALI/ARDS with HFO, but the lack of a comparison group limits further interpretations. Prospective, randomized, controlled clinical trials are needed to compare HFO to CV using strategies to increase EELV and minimize EILV in adults with ALI/ARDS.

Conclusion

Numerous studies have suggested that CV may perpetuate or exacerbate lung injury by delaying or preventing recovery from ALI/ARDS. Small VT ventilation to reduce EILV during CV recently was shown to improve mortality when compared to a more traditional VT approach.[14] There is also abundant evidence in experimental animals and, more recently, in humans to suggest that there are lung protective effects with higher EELV. While there are encouraging results with recent CV-based lung protective strategies, the potential benefits of these strategies may be limited. HFV, especially HFO, offers the best opportunity to achieve greater lung recruitment without overdistention while maintaining normal or near-normal acid-based parameters. Results of animal and pediatric studies using HFO are encouraging, but further work is necessary to determine the value and optimal use of HFO in adults with ALI/ARDS. Some studies suggest that HFV may be beneficial in patients with bronchopleural fistulas. However, this gross manifestation of vo-

lutrauma is uncommon (it occurs in approximately 10% of patients with ALI/ARDS) and is not significantly associated with increased mortality.[104] Thus, the extra costs of using HFO (new equipment purchase and training of personnel for a small proportion of patients who have ALI/ARDS) are not yet justified in the absence of evidence that HFO will improve important clinical outcomes. Until the results of well-designed studies demonstrate that HFO is superior to CV, the use of HFO should be considered a promising but experimental mode of ventilation for patients with ALI/ARDS.

ACKNOWLEDGMENT: The authors thank Henry E. Fessler, MD, for assistance with artwork.

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