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High-Frequency Oscillatory Ventilation

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Introduction

Data supporting the feasibility of high-frequency oscillatory ventilation (HFOV) come from the observation that delivering very tidal volumes small at high frequencies can overcome the need for adequate bulk gas flow in the lung. In the early 1970s, while attempting to measure cardiac performance in large animals by assessing the myocardial response to pericardial pressure oscillations, Lunkenheimer and colleagues found that endotracheal high-frequency oscillations could produce efficient CO_2 elimination in the absence of significant chest wall excursion [1,2]. These investigators determined that CO_2 elimination was related to changes in the frequency of oscillation as well as the amplitude of the vibrations [1]. In general, CO_2 was cleared optimally at a frequency between 23–40 Hz, with smaller animals requiring higher frequencies [1]. Several years later, Butler and colleagues observed that gas exchange could be supported in humans at a frequency of 15 Hz, hypothesizing that this would enhance diffusive gas transport while minimizing dependence on bulk convective gas flow in the airways [3]. In their study, a series of patients, 9 years of age and older, were successfully ventilated with a piston pump calibrated to deliver tidal volumes in the range of 50–150 mL, and a single 2.5-kg infant was supported with a tidal volume of 7.5 mL using the same device [3].

At the moment, there are many laboratory data to suggest that repetitive cycles of pulmonary recruitment and derecruitment are associated with identifiable markers of lung injury, and experimental models of ventilatory support that reverse atelectasis, limit phasic changes in lung volume, and prevent alveolar overdistension appear to be less injurious [4–11]. There is also a growing quantity of clinical data that support these observations. A recent single-center cohort study demonstrated that among 332 patients who did not have acute lung injury (ALI) at initiation of mechanical ventilation, 80 (24%) developed it within 5 days [12]. Approximately one third of the study patients were ventilated using tidal volumes exceeding 12 mL/kg, and multivariate analysis identified large tidal volumes as the most significant risk factor for the development of ALI (odds ratio 1.3 for each 1 mL above 6 mL/kg; $p < 0.001$)[12].

Inappropriate mechanical ventilation strategies may also potentiate the dysfunction of distant organs among patients with respiratory failure. In a multicenter trial, Ranieri and colleagues randomized 37 patients to receive a strategy directed at ventilating between the upper and lower inflection points on the pressure–volume curve (Figure 9.1), versus a higher volume, lower peak end-expiratory pressure (PEEP) strategy targeted at achieving normal blood gas tensions in the control group [6]. Bronchoalveolar lavage (BAL) and blood samples showed a local and systemic inflammatory cytokine response at 36 hr among those in the control group, whereas the experimental strategy appeared to diminish this response [6]. In addition, a landmark multicenter trial has brought about the understanding that specific strategies for mechanical ventilation can have an important influence on outcomes in patients with the acute respiratory distress syndrome (ARDS). In 2000, the ARDS Network investigators demonstrated a 22% relative reduction in mortality among adult patients with ARDS on conventional mechanical ventilation who were randomized to receive relatively small tidal volumes (6 mL/kg ideal body weight) compared with those who were ventilated with larger tidal volumes (12 mL/kg ideal body weight) [13]. Collectively, these observations on the benefits of tidal volume reduction have led to the expectation that high-frequency ventilation would have an important role in the clinical arena because of its unique ability to provide adequate gas exchange using very low tidal volumes in the setting of continuous alveolar recruitment. Theoretically, high-frequency ventilation provides the ultimate *open-lung* strategy of ventilation, preserving end-expiratory lung volume, minimizing cyclic stretch, and avoiding parenchymal overdistension at end inspiration by limiting tidal volume and transpulmonary pressure (Figure 9.2) [4–7].

Modalities of High-Frequency Ventilation

The major modalities of high-frequency ventilation include high-frequency flow interruption (HFFI), high-frequency positive pressure ventilation (HFPPV), high-frequency jet ventilation (HFJV),

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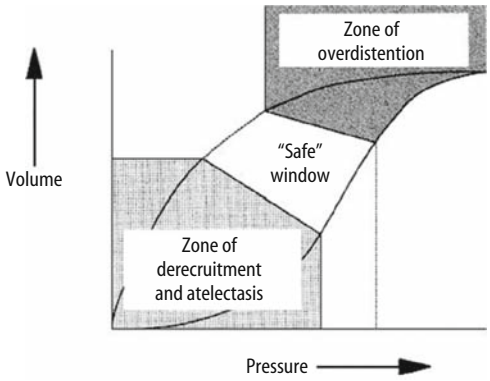

Figure 9.1. Pressure–volume relationships in acute lung injury. High end-expiratory pressures and small tidal volumes minimize the potential for derecruitment (lower left) and overdistension (upper right). (From Froese AB. High-frequency oscillatory ventilation for adult respiratory distress syndrome: let's get it right this time! Crit Care Med 1997;25:906–908. Copyright 1997. Reprinted with permission from Lippincott Williams & Wilkins.)

and high-frequency oscillatory ventilation (HFOV). High-frequency oscillatory ventilation is the most widely used form of high-frequency ventilation in clinical practice today. In HFOV, lung recruitment is maintained by the application of relatively high mean airway pressure, while ventilation is achieved by superimposed sinusoidal pressure oscillations that are delivered by a motor-driven piston or diaphragm at a frequency of 3–15 Hz [7,14]. High-frequency oscillatory ventilation is the only form of high-frequency ventilation in which expiration is an active process. As a result, alveolar ventilation is achieved during HFOV with the use of tidal volumes in the range of 1–3 mL/kg, even in the most poorly compliant lungs [14].

Gas Transport and Control of Gas Exchange

A comprehensive understanding of the mechanisms of gas transport in HFOV has not emerged despite a long period of scientific investigations. Although direct bulk flow can account for ventilation of proximal alveolar units even at very low tidal volumes, it is now believed that *Pendelluft*, or mixing of gases among alveolar units with varying time constants, contributes significantly to gas exchange at high frequencies [15–17]. In addition, efficient gas mixing likely occurs along the parabolic inspiratory gas front in high-frequency oscillation, because this provides an increased area along which radial diffusion can occur [15,16]. Finally, axial asymmetry of inspiratory and expiratory gas flow profiles creates separation of fresh gas and exhaled gas so that inspiratory gas flow travels down the central axis of the airway, while expiratory flow is distributed along the airway wall [15,16].

Experimental work in healthy rabbits has shown that CO_2 elimination during HFOV is a function of frequency and the square of the tidal volume ($V_{CO2} = f \times Vt^2$) [18]. In HFOV, tidal volume is positively correlated with the amplitude of oscillation ("delta P," ΔP), and is related inversely to the frequency (Hz) [19]. Alveolar recruitment is positively correlated with the mean airway pressure (Paw) and the ratio of inspiratory time to expiratory time (I:E) [20]. Although most of the research using HFOV has focused on the use of higher frequency ranges, CO_2 elimination can probably occur at many potential combinations of f and Vt^2, with higher frequency ranges providing conditions of lowest lung impedance and, consequently,

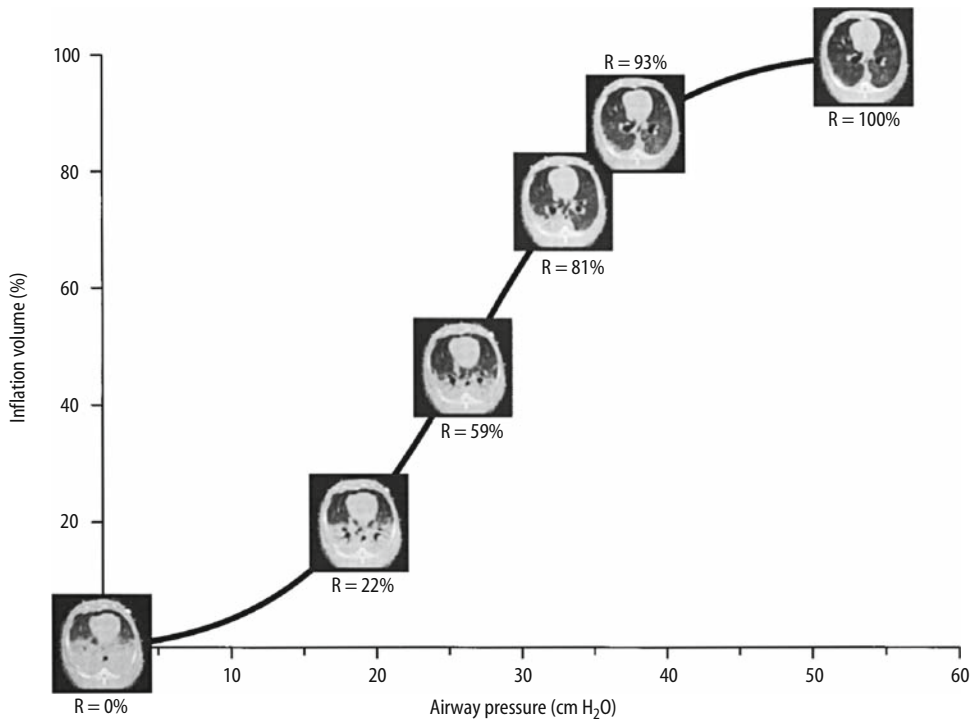

Figure 9.2. Open lung strategy in ARDS: alveolar recruitment along the pressure–volume curve in a large animal experimental model of ARDS, showing substantial increases in aeration of dependent lung units. R indicates percentage of total recruitment occurring at the corresponding airway pressure. At high airway pressures, nondependent regions may be vulnerable to overdistension. (From Gattinoni et al. [68]. Copyright 2001 the American Thoracic Society. Reprinted with permission.)

a lower pressure cost of ventilation [21,22]. In HFOV, Paw, ΔP, frequency, and I:E are all directly controlled by the operator.

Presently available high-frequency ventilators vary with respect to pressure waveforms, consistency of I:E ratio over a range of frequencies, and the relationship of displayed mean airway pressure to distal mean alveolar pressure [19]. Most of the experience with HFOV in the clinical arena involves the SensorMedics 3100A (SensorMedics, Yorba Linda, CA), which is approved for use in infants and children. Almost 20 years of study using this device in the laboratory have provided clinicians with a fundamental understanding of its performance characteristics. Using in vitro models as well as alveolar capsule techniques in small animals with open chests, several investigators have reported that mean airway pressure and ΔP are significantly attenuated by the tracheal tube, that alveolar pressure is inhomogeneously distributed during HFOV, and that the I:E ratio is an important determinant of alveolar pressure [20,23–25]. Specifically, early data from surfactant-deficient small animals, as well as from large animals and humans, seemed to indicate that limitation of expiratory time using an I:E ratio of 1:1 would promote alveolar gas trapping, especially at lower mean airway pressures [20,26–28]. This observation led to the suggestion that HFOV be applied in the clinical setting with an I:E ratio of no greater than 1:2.

When transitioning the patient to HFOV from conventional ventilation (Figure 9.3), the Paw on HFOV is typically set up to 5 cm H_2O above the Paw last used on the conventional ventilator in order to maintain recruitment in the face of pressure attenuation by the tracheal tube. Amplitude (ΔP) is set by adjusting the power control while observing for adequacy of chest wall vibrations, as indicated by visible vibration to the level of the groin. Frequencies of 12–15 Hz are generally used for small infants, whereas lower frequencies in the range of 3–8 Hz are typically used for larger pediatric patients and adults, with the goal of generating enough volume displacement to adequately ventilate using currently available HFOVs. If employing an *open lung* ventilation strategy, Paw is then slowly titrated upward in 1–2 cm H_2O increments, with the goal of reducing the FiO_2 to ≤0.6 with an arterial oxygen saturation of ≥90%.

Achieving acceptable oxygen saturations at this stage will often require intravascular volume expansion in order to avoid creating *zone 1* conditions [29] in the lung as pulmonary blood volume is displaced by the increasing alveolar pressure. Once adequate alveolar recruitment is achieved, it may be possible to capitalize on pulmonary hysteresis, evident in many regions of the lung early in the course of disease (see Figure 9.1) [30], by carefully adjusting the Paw downward as long as the oxygenating efficiency is preserved. Alternatively, after a brief period of aggressive volume recruitment, the Paw can be dropped to a point that is known to be above the closing pressure, with the expectation that adequate tidal volume will be preserved [30]. Adequacy of lung recruitment is verified by ensuring that both hemidiaphragms are displaced to the level of the ninth posterior rib on chest x-ray [14]. A typical sequence of steps for addressing hypercarbia once an appropriate degree of lung inflation as well as patency of the tracheal tube are verified would be (1) increasing the ΔP in increments of 3 cm H_2O until power is maximized, (2) decreasing the frequency in increments of 0.5–1 Hz, and (3) partially deflating the tracheal tube cuff, if available, to allow additional egress of CO_2 [31–33]. In the latter case, any decrement in Paw should be corrected by increasing the bias flow as necessary to maintain a stable level of distending pressure [32,33].

If employing a strategy targeted at managing active air leak, the lung is initially recruited using stepwise increases in Paw to achieve FiO_2 ≤0.6 and SaO_2 ≥90%, and then Paw and ΔP are lowered to a point just below the *leak pressure*, the value at which air is no longer seen to drain from the thoracostomy tube. If the leak pressure is relatively low, it may be necessary to tolerate an FiO_2 in excess of 0.6 with SaO_2 ≥85%, and hypercarbia if necessary, as long as pH ≥7.25, in order to provide satisfactory gas exchange while minimizing alveolar pressure [17,34–36]. As demonstrated in a small animal model of pneumothorax, higher frequencies and short inspiratory times may also minimize air leak during HFOV [36].

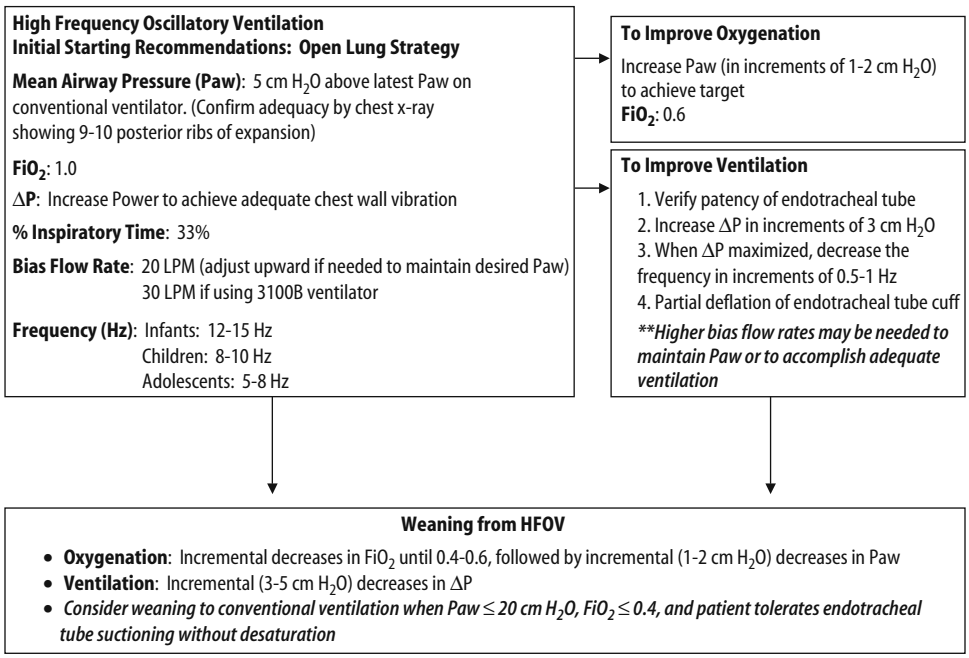

Figure 9.3. Transitioning the critically ill child from conventional mechanical ventilatory support to high-frequency oscillatory ventilation.

High-Frequency Oscillatory Ventilation in the Neonate and Infant

Neonatal Respiratory Distress Syndrome

Surfactant deficiency, high chest wall compliance, and a dynamic functional residual capacity (FRC) that is near closing volume in the preterm infant interact to potentiate a repetitive cycle of derecruitment and reinflation that makes the neonatal lung particularly well suited to an open lung strategy of ventilation (Figure 9.4). Following laboratory investigations that demonstrated adequate gas exchange at lower intrapulmonary pressures and reduced incidence of pulmonary air leak with the use of HFOV in surfactant-deficient small animals [37,38], a substantial amount of data have accumulated on the use of HFOV in humans for the management of the neonatal respiratory distress syndrome (RDS).

The first large randomized, controlled trial with premature infants comparing high-frequency ventilation using a piston oscillator with conventional mechanical ventilation was published in the pre-surfactant era by the HIFI Study Group in 1989 [39]. The study was designed to evaluate the effect of high-frequency ventilation on the incidence of chronic lung disease of prematurity and included 673 infants weighing 750–2,000 g who had been supported less than 12 hr on conventional ventilation for respiratory failure in the first 24 hours of life. Infants randomized to receive HFOV were administered an FiO_2 and Paw equal to those administered on conventional ventilation. Infants who had not already been tracheally intubated were administered an FiO_2 equal to that received before intubation and a Paw of 8–10 cm H_2O. Hypoxemia was first addressed by increasing the FiO_2 and then by increasing the Paw [39]. Overall, the investigators did not incorporate alveolar recruitment into the HFOV strategy, and the study was unable to show a significant difference in the incidence of chronic lung disease or in 28-day mortality between the two groups. However, it did show a significant increase in the incidence of air leak as well as high-grade intraventricular hemorrhage among the infants who were randomized to receive HFOV [39].

Two additional large multicenter trials were recently published in an effort to clarify the role of high-frequency ventilation in the management of RDS in preterm infants [40,41]. Unlike the HIFI trial and subsequent studies that produced conflicting results [42,43], these two trials were produced by centers with a great deal of experience with the use of HFOV in neonates, and each emphasized alveolar recruitment as part of the strategy for high-frequency ventilation. In a well-controlled study, Courtney and colleagues used a strategy in the conventional ventilation arm that targeted a tidal volume of 5–6 mL per kg body weight and ventilated infants in the HFOV arm at a frequency of 10–15 Hz [40]. These investigators were able to show that infants randomized to receive HFOV with the 3100A were successfully separated from mechanical ventilation earlier than those assigned to a lung-sparing strategy of conventional ventilation, and, among the infants assigned to high-frequency ventilation, there was a significant decrease in the need for supplemental oxygen at 36 weeks postmenstrual age [40]. By defining a disease threshold in the study infants, adhering to lung-protective protocols for mechanical ventilation, and extubating from the assigned ventilator according to specific criteria, this study identified a set of circumstances in which HFOV may be used with clear benefit in preterm infants with RDS [40]. In contrast, Johnson and colleagues included healthier patients, used fewer defined protocols, and used more aggressive ventilator strategies [41]. In both study arms, the investigators targeted a $PaCO_2$ of 34–53 torr, whereas Courtney and colleagues used a ventilation strategy that allowed permissive hypercapnia [40]. For those infants who were supported on HFOV, Johnson and colleagues initiated therapy at a frequency of 10 Hz, and, if maximizing amplitude (ΔP) did not achieve adequate clearance of CO_2, the frequency was subsequently reduced [41]. Finally, Johnson's group transitioned the majority of

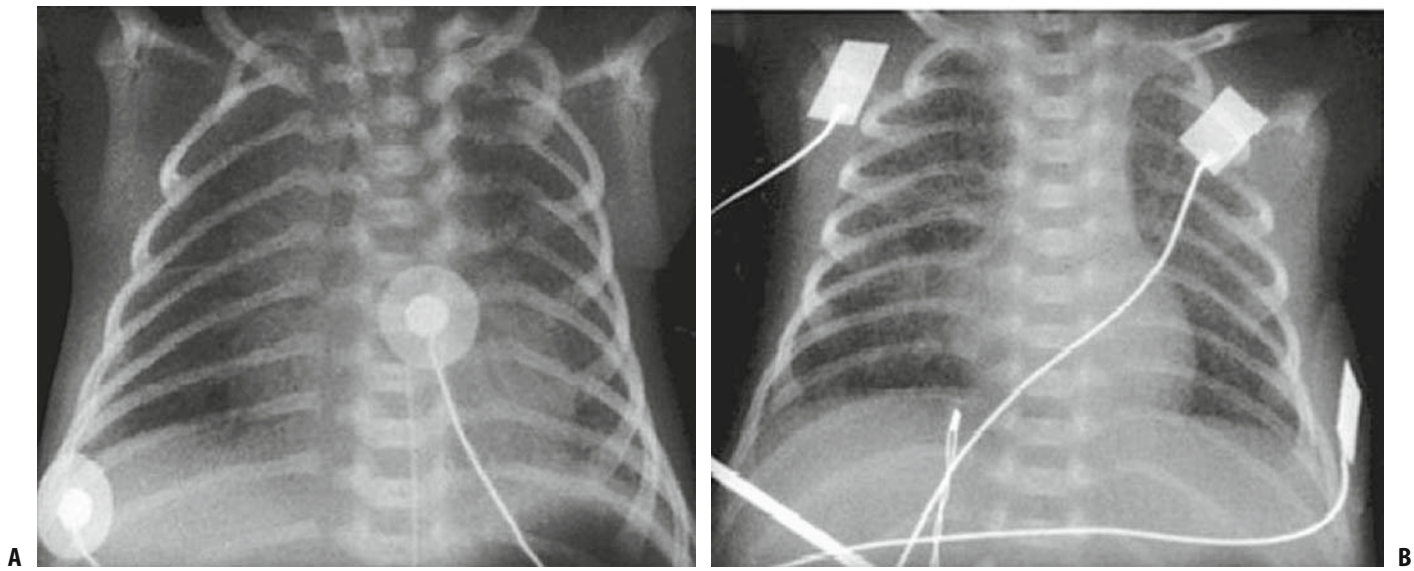

Figure 9.4. Conventional ventilation versus high-frequency oscillatory ventilation (HFOV) in the preterm neonate: representative chest radiographs from preterm infants with the respiratory distress syndrome assigned to receive HFOV or conventional ventilation. Each picture is taken on day 2 of mechanical ventilatory support. **(A)** Conventional ventilation. (**B**) High-frequency oscillatory ventilation. (*Source:* Helbich TH, Popow C, Dobner M, Wunderbaldinger P, Zekert M, Herold CJ. New-born infants with severe hyaline membrane disease: radiological evaluation during high-frequency oscillatory versus conventional ventilation. Eur J Radiol 1998;28:243–249. Copyright 1998 with permission.)

study infants to conventional ventilation for weaning after a median time on HFOV of 3 days, a relatively small portion of the total duration of mechanical ventilation [41].

It is important to emphasize that neither of these studies was able to duplicate the findings of the HIFI group with respect to associating the use of HFOV with the development of high-grade intraventricular hemorrhage. However, the difference in outcomes in the two trials is striking. The rigorously controlled conditions in the Courtney study probably isolate the effect of HFOV with greater clarity, and their data suggest that only 11 infants need be supported with HFOV in order to prevent one occurrence of chronic lung disease at 36 weeks postmenstrual age [40]. Using Johnson's data, the number of infants needed to support on HFOV in order to prevent one occurrence of chronic lung disease is 50 [41]. Although the study design used by Johnson and colleagues may better represent actual practice, the outcomes indicate that exposure to aggressive conventional ventilation protocols may offset the benefits of HFOV.

Congenital Diaphragmatic Hernia

Infants with congenital diaphragmatic hernia (CDH) commonly demonstrate complex pulmonary pathophysiology that derives from alveolar and pulmonary vascular hypoplasia [44]. The discovery that ventilator-induced lung injury is evident on histopathology specimens from these patients [45,46] has continued to focus attention in recent years on applying lung-protective strategies of mechanical ventilation to infants with CDH. As a result, numerous centers have reported case series of infants with CDH in whom the application of high-frequency oscillatory ventilation has been associated with an improvement in survival [47–49]. Several retrospective studies of HFOV in infants with CDH have also reported improved survival, with dramatic reductions in $PaCO_2$ and concurrent improvements in oxygenation [48,49]. At least one center using HFOV without the use of extracorporeal membrane oxygenation (ECMO) in infants with CDH has reported an overall survival rate comparable to that of infants who were supported with conventional ventilation and ECMO, although no survival benefit specifically attributable to the use of HFOV was identified [45]. Nonetheless, some of the best survival statistics for CDH are reported in one recent single-center historical experience in which these infants were managed with conventional ventilation. This report documented a significant increase in survival from 44% to 69% among all infants with this condition during a period in which flow-triggered pressure support ventilation with permissive hypercapnia was used. Even higher survival rates were noted in those without coexisting heart disease [50].

Overall the role of HFOV in the management of infants with CDH is unclear. Despite its theoretical advantages in maintaining alveolar recruitment with minimal pressure cost, application of an open lung strategy using high-frequency ventilation in infants with CDH can lead to problems because aggressive recruitment in the setting of alveolar hypoplasia may precipitate acute increases in pulmonary vascular resistance with ensuing hemodynamic instability, air leak, or ongoing lung injury. Centers that report success with HFOV in the management of infants with CDH have found that it is important to limit Paw to $\leq$20 cm H_2O in order to avoid alveolar overdistension [17]. In summary, infants with CDH may suffer excess lung injury if aggressively ventilated in an attempt to manipulate pulmonary vascular resistance, and the use of high-frequency ventilation to achieve specific short-term physiologic end-points may not offset this risk.

Persistent Pulmonary Hypertension of the Newborn

Several investigators have tested the hypothesis that sustained alveolar recruitment using HFOV could enhance the delivery of therapeutic gases to patients with respiratory failure. In one large multicenter trial, therapy with HFOV was coupled with inhaled nitric oxide (iNO) in an effort to identify the relative contribution of each therapy to outcomes in patients with persistent pulmonary hypertension of the newborn (PPHN). The investigators randomized 200 neonates with severe hypoxic respiratory failure and PPHN to receive therapy with HFOV alone or conventional ventilation combined with iNO [51]. Crossover as a result of treatment failure resulted in combined therapy with HFOV and iNO. The study concluded that significant short-term improvements in PaO_2 occurred during combined treatment with HFOV and iNO among patients who failed either therapy alone [51]. This combination was particularly effective among patients with severe parenchymal disease attributable to RDS and meconium aspiration [51]. The suggestion that efficacy of iNO may depend on the adequacy of alveolar recruitment is also supported by a retrospective analysis of data from children enrolled in a multicenter randomized trial of the use of iNO in the treatment of acute hypoxic respiratory failure [52].

Air Leak Syndromes

Given the expectation that satisfactory gas exchange occurs at a relatively low Paw during HFOV, it is not surprising that this therapy has been applied with success in severe air leak syndromes. In one early case report, 27 low-birth-weight infants (mean birth weight 1.2 kg) who developed pulmonary interstitial emphysema on conventional ventilation were transitioned to HFOV. All demonstrated early improvement on HFOV, and survivors demonstrated sustained improvements in oxygenation and ventilation, allowing for lower Paw and FiO_2 and ultimate resolution of air leak. Overall survival among nonseptic patients was 80% [53].

Bronchiolitis

Despite concerns that ventilation at high frequencies may exacerbate dynamic air trapping in diseases of the lower airways, HFOV has been used in the management of bronchiolitis caused by respiratory syncytial virus [54,55]. A couple of small case series have reported the successful application of HFOV using an open lung strategy in young infants with bronchiolitis [54,55]. Applying a relatively high Paw in this clinical context derives from the observation that lower Paw may promote worsening hyperinflation by creating *choke points* that impede expiratory flow [28]. The investigators used a frequency of 10–11 Hz and an I : E of 0.33, with initial pressure amplitude (ΔP) in the 35–50 cm H_2O range. All patients survived without development of pneumothoraces attributable to HFOV and without need for ECMO [54,55].

High-Frequency Oscillatory Ventilation in the Child

Diffuse Alveolar Disease

Much of the data on the application of HFOV outside of the neonatal period comes from case series in which this therapy was applied to children with acute severe respiratory failure attributable to diffuse alveolar disease and/or air leak syndromes. In the early 1990s, two

centers reported the use of HFOV in pediatric patients with these conditions who had been managed on conventional ventilation for varying periods of time [35,56]. In general, each concluded that HFOV may be applied safely as rescue therapy for pediatric patients with severe hypoxic lung injury and that its use is associated with improvement in physiologic end-points such as $PaCO_2$ and oxygenation index, OI = (Paw × FiO_2)/PaO_2) × 100. In addition, there were no reports of worsening air leak [35,56]. Each of these studies applied HFOV after recruiting the lung, but one of them [35] modified the HFOV protocol for patients with active air leak by dropping the Paw below the leak pressure following recruitment, raising the FiO_2 as necessary to maintain adequate oxygenation, and tolerating hypercarbia as long as the arterial pH remained above 7.25.

The first and largest multicenter randomized trial evaluating the effect of HFOV on respiratory outcomes in pediatric patients is a crossover study that enrolled patients with diffuse alveolar disease and/or air leak [34]. The investigators randomized 70 patients to receive conventional ventilation using a strategy to limit peak inspiratory pressure, or HFOV at a frequency of 5–10 Hz, using an open lung strategy in which the lung volume at which optimal oxygenation occurred was defined (SaO_2 ≥90% and FiO_2 <0.6), and, in patients with air leak, airway pressure was then limited while accepting preferential increases in FiO_2 to achieve saturations of ≥85% and pH ≥7.25 until it resolved [34]. The study found no difference in survival or duration of mechanical ventilatory support between the two groups, but significantly fewer patients randomized to receive HFOV remained dependent on supplemental oxygen at 30 days compared with those who were randomized to receive conventional ventilation, despite the use of significantly higher Paw in the HFOV group [34]. The OI, used often in the pediatric literature to quantify oxygenation failure, was shown in this study to discriminate between survivors and nonsurvivors after 24 hours of therapy. In addition, the time at which changes in OI were noted to occur influenced the likelihood of survival: an OI ≥42 at 24 hr predicted mortality with an odds ratio of 20.8, sensitivity of 62%, and specificity of 93% [34]. Post hoc analysis revealed that outcome benefits were not as great for those who crossed over to the HFOV arm [34], supporting the suggestion by numerous studies that HFOV may be most successful if employed early in the course of disease, using a strategy that emphasizes alveolar recruitment [9,37,56–58].

Other Conditions

Experience with the use of HFOV for treatment of lower airways disease in older pediatric patients is limited. In one interesting case report, HFOV was successfully applied to a toddler with status asthmaticus [59]. The authors achieved optimal CO_2 clearance using an *open lung* strategy with Paw 20 cm H_2O, low frequency (6 Hz), I:E 0.33, and relatively high ΔP (65–75 cm H_2O in the first 24 hr of therapy) without apparent air leak [59]; however, the use of HFOV in obstructive lung diseases must be considered thoughtfully.

High-Frequency Oscillatory Ventilation in the Adolescent and Adult

In recent years, the 3100B HFOV (SensorMedics, Yorba Linda, CA) has become available for use in larger pediatric patients and adult patients, addressing initial reports with large animals that adequate alveolar ventilation could not be achieved using the 3100A model [60,61]. The 3100B differs from the 3100A model by having a higher maximal bias flow, which allows for the delivery of higher mean airway pressures. The 3100B also has a more powerful electromagnet, which produces faster acceleration to maximal oscillatory pressure (ΔP) [33].

Early experiences with the use of HFOV on adolescent and adult patients with hypoxic respiratory failure are summarized in several case series [33,62]. In each, low-frequency (maximum 5–6 Hz) HFOV with a strategy of volume recruitment was used as rescue therapy for patients with ARDS who were failing conventional ventilation. These studies included patients with severe disease, including mean values for PaO_2/FiO_2 in the 60 range at the time of enrollment [33,62]. Although neither study was powered to measure significant differences in outcomes such as mortality, the majority of patients in the two studies demonstrated an improvement in short-term physiologic variables such as FiO_2, PaO_2/FiO_2 ratio, and OI [33,62]. Nonsurvivors in each of these studies were exposed to significantly longer periods of conventional ventilation, suggesting once again the importance of instituting HFOV early in the course of disease.

A multicenter, prospective, randomized controlled trial designed to evaluate the safety and effectiveness of HFOV compared with conventional ventilation in the management of early ARDS (PaO_2/FiO_2 ≤200 while on PEEP 10 cm H_2O) in adult patients was published in 2002 [32]. Treatment strategies for both arms of the study included a volume recruitment strategy and were directed at achieving SaO_2 ≥88% on FiO_2 ≤60%. Patients in the conventional arm were managed in the pressure-control mode, targeting a delivered tidal volume of 6–10 mL/kg actual body weight, without specific attention to plateau pressures. Patients in the HFOV arm were ventilated at frequencies of 3–5 Hz and were transitioned back to conventional ventilation when FiO_2 ≤0.5 and Paw ≤24 cm H_2O with SaO_2 ≥88%, and conventional ventilation was reinstituted at an equivalent Paw [32]. With regard to short-term physiologic measures, these investigators also reported a significantly higher Paw among patients on HFOV and significant early increases while on HFOV in PaO_2/FiO_2 [32]. Post-study multivariate analysis also revealed that the trend in OI was the most significant post-treatment predictor of survival regardless of treatment group—survivors showed a significant improvement over the first 72 hr of the study period and nonsurvivors did not [32]. Although the OI is not a measure traditionally reported in the adult literature, it has been reported by others as predictive of mortality in adult ARDS [62].

This study was not powered to evaluate differences in mortality between the two groups, but there was a clear trend toward increased 30-day mortality among the patients randomized to receive conventional ventilation versus those who received HFOV (52% vs. 37%) [32]. At the moment, it is not known if HFOV using low frequencies is as protective as ventilating at a higher frequency range, such as what has been used with success in small animals and human infants. It is important to understand that laboratory experiments using the 3100B HFOV have demonstrated that tidal volumes approaching those used in conventional ventilation are produced under conditions of low-frequency and high-pressure amplitude (ΔP) [63].

Adjuncts: Noninvasive Assessment of Lung Volume

One of the difficulties facing intensive care clinicians is that evaluation of the adequacy of recruitment after initiating HFOV and in response to changes in ventilator settings must be guided by

indirect measures such as peripheral oxygen saturations, fractional inspired oxygen concentration, blood gas tensions, anteroposterior chest radiographs, and a visual assessment of chest wall vibration. Global measures of alveolar plateau pressure, tidal volume, and pulmonary mechanics that are available from breath to breath when using conventional ventilation are not provided on the high-frequency ventilator console, and the operator must often use intuition when adjusting ventilator settings, risking sudden and clinically significant derecruitment or alveolar overdistension. In recent years, respiratory impedance plethysmography (RIP) and electrical impedance tomography (EIT) have emerged as two promising means by which pulmonary mechanics and alveolar recruitment can be assessed noninvasively at the bedside during HFOV.

Respiratory impedance plethysmography is a monitoring technique that is capable of quantifying global lung volume by relating it to measurable changes in the cross-sectional area of the chest wall and the abdominal compartment. In RIP, two elastic bands with Teflon-coated wires embedded in a zigzag distribution along their circumference are applied to the patient. One is typically placed around the chest, 3 cm above the xiphoid process, and the other is typically placed around the abdomen. Each of these two bands produces an independent signal, and the sum of the two signals is calibrated against a known volume of gas. Use of this technique in association with HFOV has been validated in animal models [64,65]. In a large animal model of acute lung injury managed with HFOV, Brazelton and colleagues have demonstrated that RIP-derived lung volumes correlated well with those that were obtained using a supersyringe ($r^2 = 0.78$) and that RIP is capable of tracking global changes in lung volume and creating a pressure–volume curve during HFOV [64]. With a newborn animal model, Weber and colleagues were able to demonstrate that RIP is capable of detecting relative changes in pulmonary compliance that were induced by saline lavage [65]. Experience with RIP in human subjects is limited to investigations of its application in conventional phasic ventilation. One study with adult patients [66] and another with pediatric patients [67] have utilized RIP to quantify the relative degree of derecruitment that is associated with closed, *in-line* techniques for endotracheal tube suctioning compared with open suctioning techniques. Each study was able to demonstrate a potential role for RIP in tracking global changes in lung volume at the bedside.

Applying HFOV in a way that harmonizes with what computed tomography (CT) has revealed about the heterogeneity of parenchymal involvement in ARDS [68] will ultimately depend on developing noninvasive bedside technologies that are capable of identifying regional changes in lung volume and pulmonary mechanics. Computed tomography images of the lung in ARDS patients have demonstrated that, during a prolonged inspiratory maneuver, alveolar recruitment occurs all the way to total lung capacity, according to the specific time constants of individual lung units (Figure 9.5; see also Figure 9.2) [68,69]. Therefore, *ideal* settings on HFOV would be those that achieve ventilation above the lower inflection point on the regional pressure–volume curves for the majority of lung units, while avoiding overdistension in the most compliant alveoli. Electrical impedance tomography (EIT) is one technology that may be best suited to detecting regional heterogeneity at the bedside of the patient with diffuse alveolar disease.

In EIT, a series of electrodes is applied circumferentially to the patient's chest. The electrodes sequentially emit a small amount of electrical current that is received and processed by the other electrodes in the array. Receiving electrodes determine a local change in impedance based on the voltage differential calculated between the transmitting electrode and the receiving electrode. Well-aerated areas, which conduct current poorly, are associated with high impedance, whereas fluid and solid phases (including atelectatic or consolidated lung) would be associated with lower impedance [70].

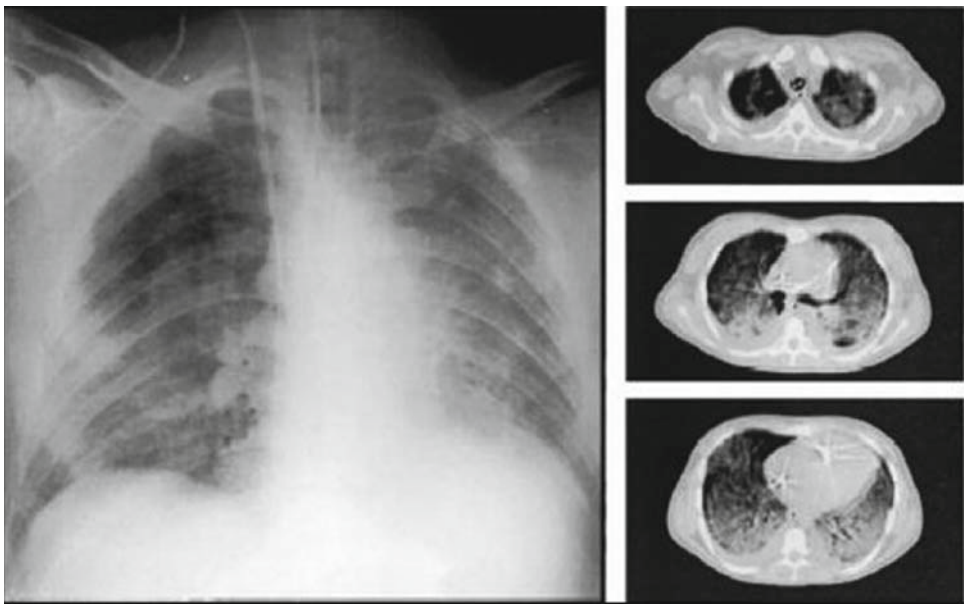

Figure 9.5. Heterogeneity of lung parenchymal involvement in acute respiratory distress syndrome (ARDS). Anteroposterior chest radiograph and computed tomography (CT) scans corresponding to lung apex, hilum, and base from a patient with sepsis and ARDS. Images are taken with the patient in the supine position at a positive end-expiratory pressure of 5 cm H_2O. The CT scans illustrate the influence of the gravitational axis on the pattern of alveolar consolidation in ARDS: nondependent regions are aerated while dependent regions remain consolidated. (From Gattinoni et al. [68]. Copyright 2001 the American Thoracic Society. Reprinted with permission.)

The impedance values that are generated are referenced to a baseline measurement and represent relative rather than absolute changes in electrical properties [69]. This process creates a tomogram that depicts the distribution of tissue electrical properties in a cross-sectional image (Figure 9.6), and the thickness of the *slice* of thorax that is represented in the image varies between approximately 15 and 20 cm, depending on the circumference of the chest [69,71]. Of the presently available EIT systems, the Goe MF II (University of Goettingen, Germany; distributed by Viasys, USA) seems to have the most favorable signal-to-noise ratio and is also capable of dynamic measurements at low lung volumes [69,72]. This system scans at a rate of 13–44 scans/sec (Hz), generating up to 44 cross-sectional images per second [69].

In the laboratory, EIT has been used in conjunction with both conventional ventilation and HFOV to describe regional lung characteristics. Investigations using conventional ventilation in large animal models of lung injury have validated EIT against supersyringe methods for the determination of regional pressure–volume (or *pressure–impedance*) curves [69,73] and have demonstrated good correlation between EIT-derived regional changes in lung impedance and CT-derived regional variations in aeration [69,74]. Using EIT to track regional lung mechanics in a large animal model of acute lung injury managed with HFOV, van Genderingen and colleagues were able to demonstrate that regional pressure–volume curves constructed using maneuvers on HFOV show less variation along the gravitational axis than pressure-volume curves that are obtained using a supersyringe method, suggesting that recruitment is more uniformly distributed between dependent and nondependent areas during HFOV [75].

Published experience with EIT in human subjects with acute lung injury or ARDS has correlated regional impedance changes induced by slow inflation maneuvers using the DAS-01P EIT system (Sheffield, UK) with regional lung density measurements obtained by CT scanning [76]. Most recently, a group of investigators at Children's Hospital Boston has utilized EIT to detect regional changes in lung volume during a standardized suctioning maneuver in children with acute lung injury or ARDS who were supported on HFOV. These data demonstrate considerable regional heterogeneity in volume changes during a derecruitment maneuver (Figure 9.7) [77].

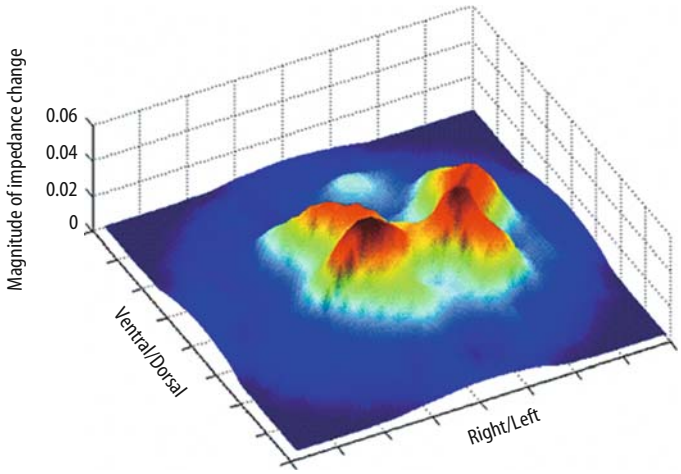

Figure 9.7. Three-dimensional depiction of recruitment after suctioning on high-frequency oscillatory ventilation. The standard deviation of impedance change after reconnection to the ventilator is displayed. (From Wolf and Arnold [77]. Copyright 2005. Reprinted with permission from Lippincott Williams & Wilkins.)

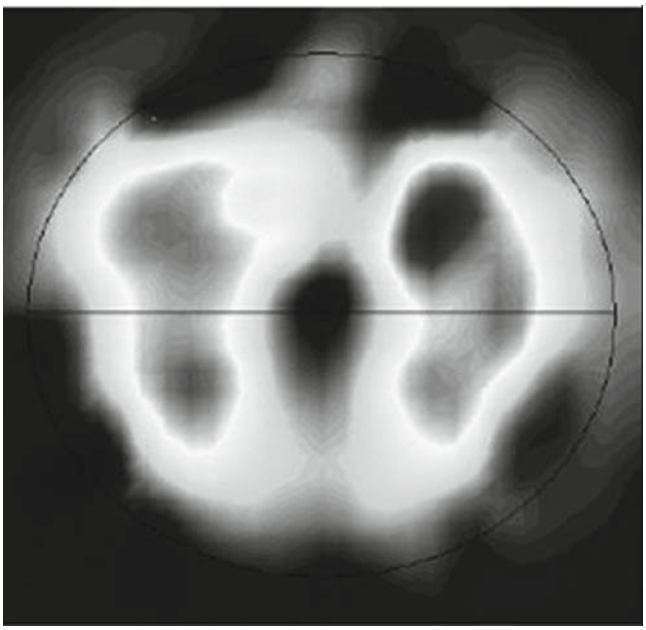

Figure 9.6. Electrical impedance tomography image of the lung. The orientation is the same as for a computed tomographic image. Both lung fields show equal impedance change during spontaneous breathing. (Courtesy of G.K. Wolf, MD. Children's Hospital Boston.)

It is tempting to expect that EIT will soon facilitate the development of strategic HFOV protocols. Theoretically, this technology can create opportunities for therapeutic intervention by dynamically tracking the regional differences in alveolar recruitment that make portions of the lung highly susceptible to ventilator-induced lung injury (VILI). However, there are important limitations to the presently available technology. For instance, substantial bias may be introduced into the EIT image because of the tendency for electrical current to follow the path of lowest impedance rather than the path of shortest distance between the transmitting and receiving electrodes [70]. This phenomenon may account in large part for the variation between EIT measures of regional lung impedance and CT measures of regional lung density [76]. In addition, because EIT measures impedance changes that are relative to baseline values, changes in baseline regional intrathoracic impedance resulting from sources other than alterations in gas volume and distribution could lead to errors in the interpretation of EIT-derived data. Despite these limitations, several investigators have reported that EIT reliably detects regional alterations in pulmonary blood flow [78] and extravascular lung water [79]. In summary, identifying a useful role for EIT as an adjunct to HFOV at the bedside will depend on additional technical modifications to make it suitable for reliably detecting very small regional tidal volumes at high frequency in the electrically hostile environment of the intensive care unit.

Weaning

Numerous studies have suggested that limiting exposure to potentially injurious strategies on conventional ventilation may enhance outcome benefits attributable to HFOV among patients with severe lung injury. Large trials in the neonatal and pediatric populations

have demonstrated favorable outcomes when HFOV is applied early in disease, and it seems logical to expect that timing the transition back to conventional ventilation may be of substantial importance as well.

Weaning a patient from HFOV may be considered when the clinician determines that gas exchange and pulmonary mechanics are suitable for transition to acceptable settings on conventional ventilation. Some investigators have reported successfully extubating infants directly from HFOV [40,41,57], but this is difficult to accomplish in the older pediatric and adult patient, who may be less likely to tolerate a degree of sedation that would allow spontaneous respiration while on HFOV and in whom spontaneous breathing may significantly depressurize the circuit, resulting in recurrent alveolar derecruitment. In general, when clinical improvement occurs to the point that Paw may be reduced to ≤20 cm H_2O, FiO2 is reduced to ≤0.4, and the patient tolerates endotracheal suctioning without significant desaturation, it is appropriate to undertake a more detailed evaluation of the patient's response to phasic ventilation provided by conventional means [17]. This may be done by hand ventilating (with the aid of an in-line pneumotachometer, if necessary) while noting the pressures, tidal volume, and inspiratory to expiratory time ratio necessary to sustain satisfactory oxygen saturation. It is common to find on transition to conventional ventilation that the patient will demonstrate satisfactory gas exchange on a mean airway pressure several cm H_2O below the last Paw on HFOV.

Conclusion

Despite compelling laboratory data supporting a physiologic rationale for HFOV in the treatment of diffuse alveolar disease, evidence of its superiority to conventional ventilation with regard to clinically important outcomes beyond the neonatal period is scant. The difficulty in proving significant clinical outcome benefit in pediatric and adult patients may be due in large part to the diverse potential etiologies of respiratory failure in these populations as well as a wide range of approaches to their medical management applied over a relatively long period of mechanical ventilatory support. It is also possible that low-frequency HFOV as traditionally used for larger patients may not be as protective as the higher frequency strategies that have been used with success in small animal models and human infants.

High-frequency oscillatory ventilation remains a therapeutic option in the intensive care unit that is worthy of further study because it is a safe and practical way to provide a "low stretch" form of ventilation that is less likely to produce VILI [4,6–9]. Applying this concept with greater precision in the clinical arena will depend on developing bedside technologies capable of both identifying the critical opening pressure in a majority of lung units and tracking regional changes in lung volume that follow changes in HFOV settings. Electrical impedance tomography is a promising technology that may ultimately be incorporated into the design of future trials that are powered to evaluate the benefits of specific HFOV protocols.

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