High Frequency Oscillatory Ventilation

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Abstract

Forty years have elapsed since investigators first appreciated that tidal volumes measuring less than the physiologic dead space can produce reliable ventilation when delivered at high frequencies. Of all high frequency ventilation techniques, high frequency oscillatory ventilation (HFOV) is the most well studied and is the most commonly utilized in clinical practice today. In HFOV, small volume oscillatory vibrations are superimposed on continuous distending pressure in a manner that allows efficient CO_2 elimination during continuous alveolar recruitment. By preserving end-expiratory lung volume, minimizing cyclic stretch, and avoiding alveolar overdistension at end-inspiration, HFOV is uniquely capable of providing the ultimate "open lung" strategy of ventilation. Over the past decade, a growing evidence base implicating phasic alveolar stretch in the pathogenesis of acute and chronic lung injury in patients with respiratory failure has driven the iterative refinement of HFOV management protocols for infants, children, and adults. The next step toward applying HFOV in a manner that takes into account the heterogeneity of parenchymal involvement in diseases such as the acute respiratory distress syndrome will require the development of non-invasive bedside technologies capable of identifying regional changes in lung volume and lung mechanics. Electrical impedance tomography (EIT) is a promising technique that could play a supporting role in the conduct of future clinical trials seeking to identify HFOV strategies that are maximally lung protective.

Keywords

High frequency oscillatory ventilation • Diffuse alveolar disease • Congenital diaphragmatic hernia • Neonatal respiratory distress syndrome • Airleak • Acute lung injury • Acute respiratory distress syndrome • Respiratory impedance plethysmography • Electrical impedance tomography • High frequency percussive ventilation

Introduction

Evidence supporting the feasibility of high frequency oscillatory ventilation (HFOV) follows from the observation that delivering very small tidal volumes at high frequencies can overcome the need for adequate bulk gas flow in the lung. While it had been appreciated years earlier that pressure oscillations could enhance oxygen diffusion [1], the stage was fully set for the dawning of the HFOV era in the early 1970s, after several investigators independently reported that applying small volume oscillatory vibrations to the airway

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efficiently eliminated CO_2, even in the absence of chest wall excursion [2–5]. The discovery was made incidentally, during experiments designed to measure cardiac or lung impedance in large animals and humans. The investigators' fortuitous decision to monitor CO_2 clearance provided the proof that ventilation with sub-dead space tidal volumes was possible. Thereafter, HFOV was recognized as a highly promising supportive care strategy, and very quickly it went on to play a major role in the global paradigm shift toward "open lung" ventilation techniques. By 1980, a series of 12 patients ranging in age from 3 days to 74 years had been successfully supported for an hour at a time, using a prototype piston pump oscillator capable of delivering tidal volumes as low as 7.5 mL, at 15 Hz [6]. In early 1983, the first pilot trial of HFOV for neonatal respiratory distress syndrome (RDS) began enrolling infants [7].

The next 30 years in this story would witness the widespread use of HFOV in neonatal intensive care units, with subsequent dissemination to pediatric and adult intensive care units. Concurrently, evidence implicating phasic alveolar stretch in the pathogenesis of acute and chronic lung injury in patients with respiratory failure has driven the iterative refinement of HFOV protocols. As of now, a large body of evidence suggests that repetitive cycles of pulmonary recruitment and de-recruitment are associated with identifiable markers of lung injury, and experimental models of ventilatory support which avoid alveolar overdistention, reverse atelectasis, and limit phasic changes in lung volume appear to be less injurious [8–15]. Chief among the major clinical trials that support this concept is the ARDS Network (ARDSNet) trial published in 2000. The ARDSNet investigators demonstrated that adults with acute lung injury or the acute respiratory distress syndrome (ARDS) who were randomized to receive a tidal volume of 6 mL/kg (predicted body weight) with plateau pressure limitation to $\leq$30 cm H_2O had a mortality reduction of 22 % relative to those ventilated with 12 mL/kg tidal volumes and allowable plateau pressures up to 50 cm H_2O [16]. This study is also one of several that would demonstrate a greater reduction in plasma levels of proinflammatory cytokines among patients who are ventilated with lower tidal volumes [10, 17, 18]. Together these studies suggest that reducing the magnitude of phasic stretch during mechanical ventilation attenuates the systemic inflammatory response and can potentially reduce the incidence of nonpulmonary organ dysfunction in patients with respiratory failure.

The long documented benefits of tidal volume reduction compel the expectation that high-frequency ventilation should have an important role in the clinical arena because of its unique ability to ventilate using subphysiologic tidal volumes and continuous alveolar recruitment. In theory, high-frequency ventilation is capable of providing 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 [8–11].

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), high frequency percussive ventilation (HFPV), and high frequency oscillatory ventilation (HFOV). HFOV remains the most widely used form of high frequency ventilation in clinical practice today. In HFOV, lung recruitment and oxygenation are maintained by the application of relatively high mean airway pressure (Paw), while ventilation is achieved by superimposed sinusoidal pressure oscillations (ΔP) that are delivered by an electromagnetically driven piston-diaphragm at a frequency of 3–15 Hz [11, 19]. HFOV is the only form of high frequency ventilation in which expiration is an "active" process. This means that CO_2 egress is facilitated by pressure gradients produced with each retrograde movement of the ventilator's piston, rather than requiring lung recoil or involvement of skeletal musculature. As a result, alveolar ventilation can be achieved during HFOV using tidal volumes in the range of 1–3 mL/kg, even in the most poorly compliant lungs [19].

Gas Transport and Control of Gas Exchange in HFOV

Many years of detailed study in the laboratory have produced an accounting of the gas transport mechanisms at work during HFOV. While direct bulk flow can be enough to ventilate proximal alveolar units during HFOV, the key advantage of high frequency techniques in facilitating gas transport throughout the lung has to do with its ability to markedly accelerate the movement of gas molecules [20]. The added velocity alters the dynamics of gas distribution in ways that facilitate gas exchange. First, during HFOV efficient gas mixing is believed to occur through radial diffusion taking place along the parabolic inspiratory gas front as it advances down the airways [20–22]. Second, shear flows created by the advancing gas front spread concentration gradients over a broad axial area, a phenomenon called "Taylor dispersion", which further facilitates diffusion. Third, "*Pendelluft*", or mixing of gases among alveolar units with varying time constants, also contributes significantly to gas exchange at high frequencies [20–23]. 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 [20–22].

In HFOV, ΔP, frequency, Paw, and I:E are all directly controlled by the operator. Experiments performed in healthy rabbits have shown that CO_2 elimination during HFOV is a function of frequency and the square of the tidal volume ($V_{CO2}=f\times Vt^2$) [24]. In HFOV, tidal volume varies directly with the amplitude of oscillation (ΔP), and varies *inversely* with the frequency (Hz) [25]. Reducing the frequency effectively lengthens the overall cycle time, which enhances CO_2 elimination at the expense of a longer inspiratory time and a higher stroke (tidal) volume. Although much of the foundational research on HFOV involved the use of higher frequency ranges, satisfactory CO_2 elimination can probably occur at many potential combinations of *f* and Vt, with higher frequency ranges providing conditions of lowest lung impedance and consequently, a lower pressure cost of ventilation [26, 27].

Alveolar recruitment during HFOV is directly related to both Paw and the ratio of inspiratory time to expiratory time (I:E) [28]. While this relationship also holds true for conventional ventilation, an important distinction between the two modalities is that HFOV delivers the Paw as a continuous distending pressure, which maximizes the alveolar surface area available for gas exchange throughout the respiratory cycle. In the injured lung, HFOV produces better oxygenation and higher mean lung volume than conventional ventilation at an equivalent Paw, *provided that the Paw is set above the lung's opening pressure* (Fig. 10.1) [29]. If HFOV is initiated early enough in the disease process that pressure-volume hysteresis is preserved, a preceding recruitment maneuver can position the lung on the deflation limb of the volume-pressure curve, where lung volume (and oxygenation) is maintained at a lower Paw. Carefully adjusting the Paw setting downward, letting it hover just above the lung's closing pressure, will exploit pulmonary hysteresis, allowing satisfactory oxygenation at the lowest possible pressure cost (Fig. 10.2). In practice, this corresponds to the lowest Paw value that maintains the oxygenation gains from the recruitment maneuver. HFOV's superior ability to capitalize on pressure-volume hysteresis is a key part of the rationale for its use in the management of diffuse alveolar disease and airleak syndromes.

Presently available high frequency ventilators vary with respect to pressure waveforms, consistency of the I:E ratio over a range of frequencies, and the relationship between displayed mean airway pressure and the actual mean alveolar pressure [25, 30, 31]. Most of the clinical experience with HFOV involves the SensorMedics 3100A (CareFusion Corporation, Yorba Linda CA), which was approved for use in neonates in 1991 and for older infants and children in 1995. More recently, the SensorMedics 3100B high-frequency oscillatory ventilator (CareFusion, Yorba Linda, CA) became available for use in larger pediatric patients (>35 kg) and adult patients. The 3100B model was approved for use outside of the US in 1998 and within the US in 2001, addressing concerns arising from large animal experiments that adequate alveolar ventilation for larger patients might not be achievable using the 3100A model [32, 33]. The 3100B differs from the 3100A model by having a more powerful electromagnet, which produces faster acceleration to maximal oscillatory pressure (ΔP). It also allows a higher maximal bias flow, which makes it possible to deliver higher mean airway pressures [34]. Many pediatric intensive care units now use the 3100A and 3100B oscillators interchangeably for older children, although operating each machine using a particular combination of settings may not produce exactly the same results in an individual patient. The automated piston centering mechanism on the current generation of 3100B oscillators was designed to counteract retrograde piston displacement when maintenance Paw is set in the range of 40–45 cm H_2O [31]. At least one group of investigators has observed that operating the 3100B using an I:E of 1:2 and a lower Paw (30 cm H_2O) can cause the piston position to shift in a way that truncates the pressure waveform, reducing tidal volume delivery below what the 3100A model would deliver at the same settings [31]. Clinicians can compensate for this phenomenon by adjusting settings as appropriate to achieve therapeutic objectives.

Years of experience gained in laboratory and clinical settings have provided clinicians with a fairly detailed understanding of each device's other important performance characteristics. Multiple lines of evidence using a variety of experimental models confirm that the endotracheal tube both distorts and dramatically attenuates oscillatory pressure waves (Fig. 10.3) and that the I:E ratio is an important determinant of how much pressure (and tidal volume) is ultimately transmitted to the alveoli [28, 31, 35–39]. Preclinical data have consistently shown that limitation of expiratory time using an I:E ratio of 1:1 promotes alveolar gas trapping. In fact, under certain conditions mean alveolar pressure can actually exceed the Paw displayed on the ventilator console [28, 30, 40–42]. This observation prompted the suggestion that HFOV be applied in the clinical setting using an I:E ratio no greater than 1:2.

Strategies for Initiating HFOV: Diffuse Alveolar Disease and Airleak

Many neonatal intensive care units now use HFOV preferentially over conventional ventilation to support the most vulnerable preterm infants with moderate to severe lung disease [43]. In older infants and children, typical indications for initiating HFOV include (1) diffuse alveolar disease without evidence of severe airflow obstruction or intracranial

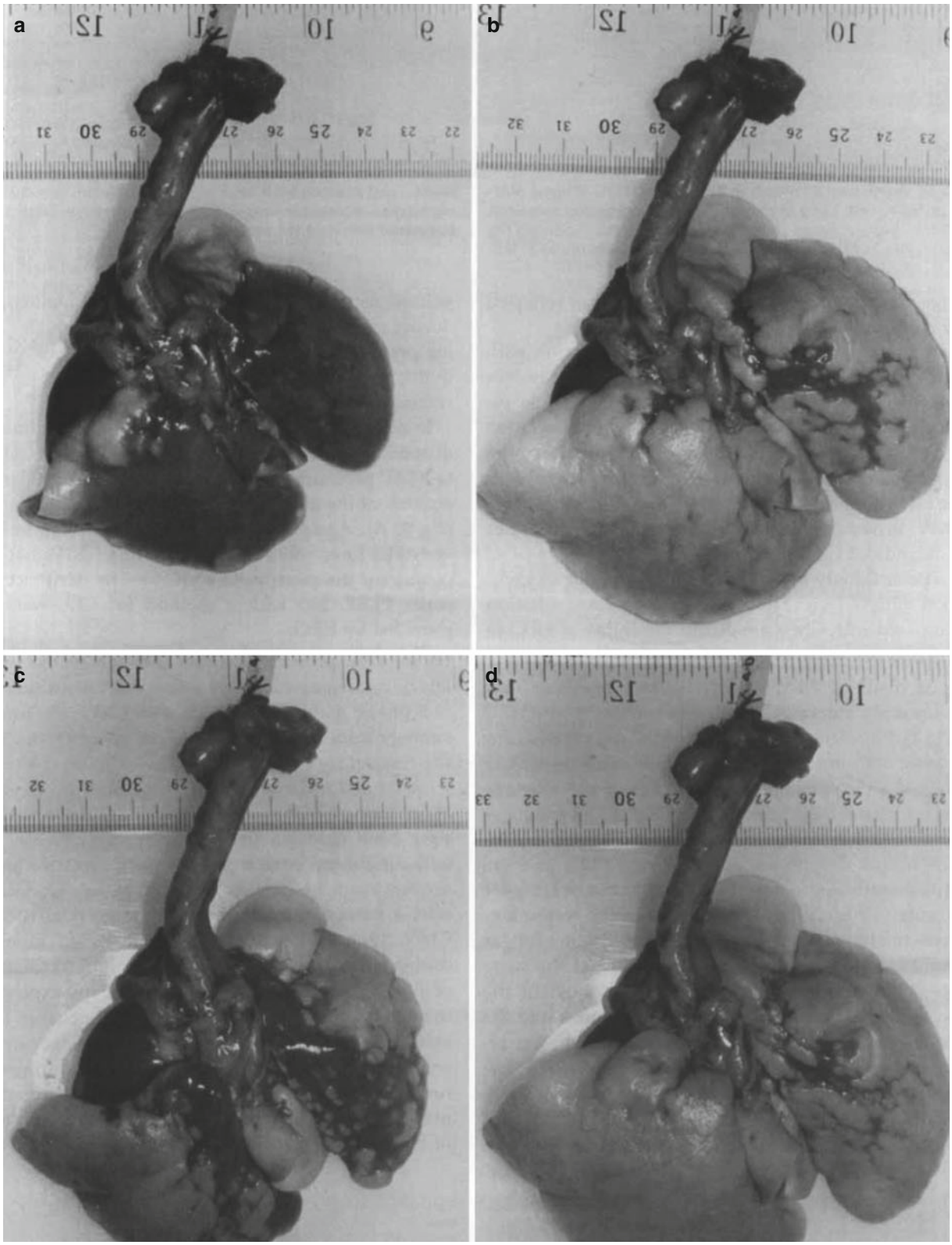

Fig. 10.1 (**a**–**d**): Lung volume during conventional ventilation (Panels **a**, **b**) compared to HFOV (Panels **c**, **d**), at equivalent mean airway pressure. Excised lungs from a rabbit lung lavage model are shown. Panel (**a**) depicts marked atelectasis at end-expiration (PEEP 9 cm H_2O). Panel (**b**) shows the lung at end inspiration; tidal volume is adjusted to produce eucapnea. Panels (**c**, **d**) depict the same lung during HFOV, using a mean airway pressure equivalent to the one represented in Panels (**a**, **b**). Panel (**c**) shows the lung during HFOV without a preceding recruitment maneuver; residual atelectasis remains apparent. Panel (**d**) shows the lung during HFOV with a preceding recruitment maneuver (Reprinted from Kolton et al. [29]. With permission from Wolter Kluwers Health)

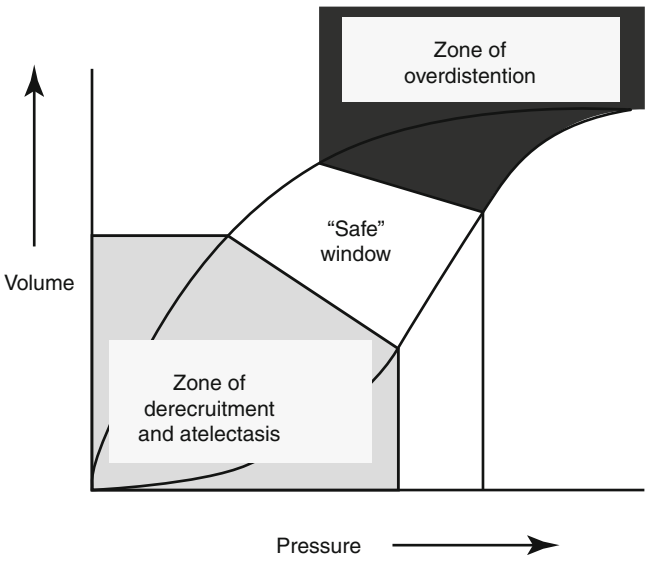

Fig. 10.2 Pressure-volume relationships in acute lung injury. High end-expiratory pressures and small tidal volumes minimize the potential for derecruitment (*lower left*) and overdistension (*upper right*). The critical opening pressure of the lung corresponds to the lower inflection point on the inspiratory limb of the volume-pressure curve. The closing pressure of the lung corresponds to the lower inflection point on the expiratory limb of the curve (Reprinted from Froese [129]. With permission from Wolter Kluwers Health)

hypertension; and (2) oxygenation failure (FiO_2 ≥0.7 and mean airway pressure ≥15 cm H_2O on conventional ventilation); or (3) ventilation failure (pH <7.25 with tidal volume ≥6 mL/kg predicted body weight and plateau pressure ≥30–35 cm H_2O) [44]. When transitioning the patient from conventional (phasic) ventilation to HFOV, 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 endotracheal tube. Amplitude (ΔP) is set by adjusting the Power control, which controls the amount of current that is delivered to the motor driving the ventilator piston. The frequency is initially set between 10 and 15 Hz for small infants. However, when initiating HFOV in children and adults, a lower frequency setting is usually necessary in order to achieve adequate ventilation. Strict age-based ranges have historically determined where clinicians set the frequency, partly out of concern that the present generation of high frequency ventilators would not be capable of generating enough volume displacement to adequately ventilate larger patients unless the frequency was drastically reduced. However, recent studies in test lung models [30], large animal models [38], and adult humans [30] have confirmed that frequency reductions have a greater impact on tidal volume delivery than amplitude increases, and tidal volumes approaching those generated

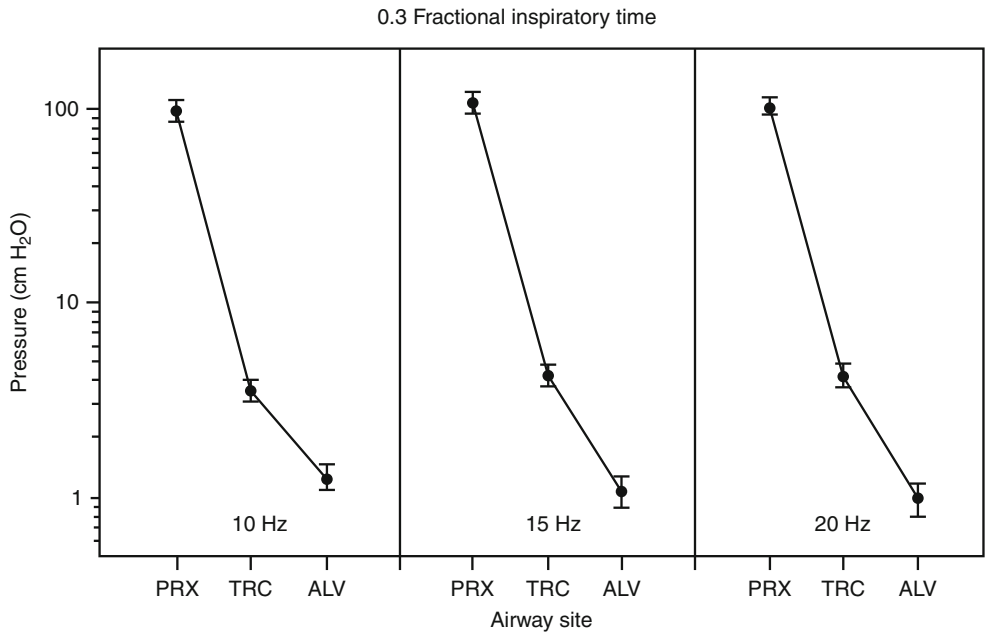

Fig. 10.3 Amplitude attenuation on HFOV, in open-chested rabbits (without lung injury): The relationship between proximal, tracheal, and alveolar amplitudes are shown at 10, 15, and 20 Hz, and %I:E 0.3 (*plotted values* represent mean peak-to-trough pressure ± SEM). Proximal pressures are measured at the airway opening. Tracheal pressures are measured 2 cm below the distal opening of the 3.0 mm (outer diameter) endotracheal tube. Alveolar pressures are measured using a pressure transducer attached to a low mass capsule mounted on the pleural surface. Panels depict significant, progressive amplitude attenuation across the endotracheal tube, from airway opening ("*PRX*") to trachea ("*TRC*") and down to the alveolus ("*ALV*") ($p<0.0001$) (Reprinted from Gerstmann et al. [35]. With permission from Nature Publishing Group)

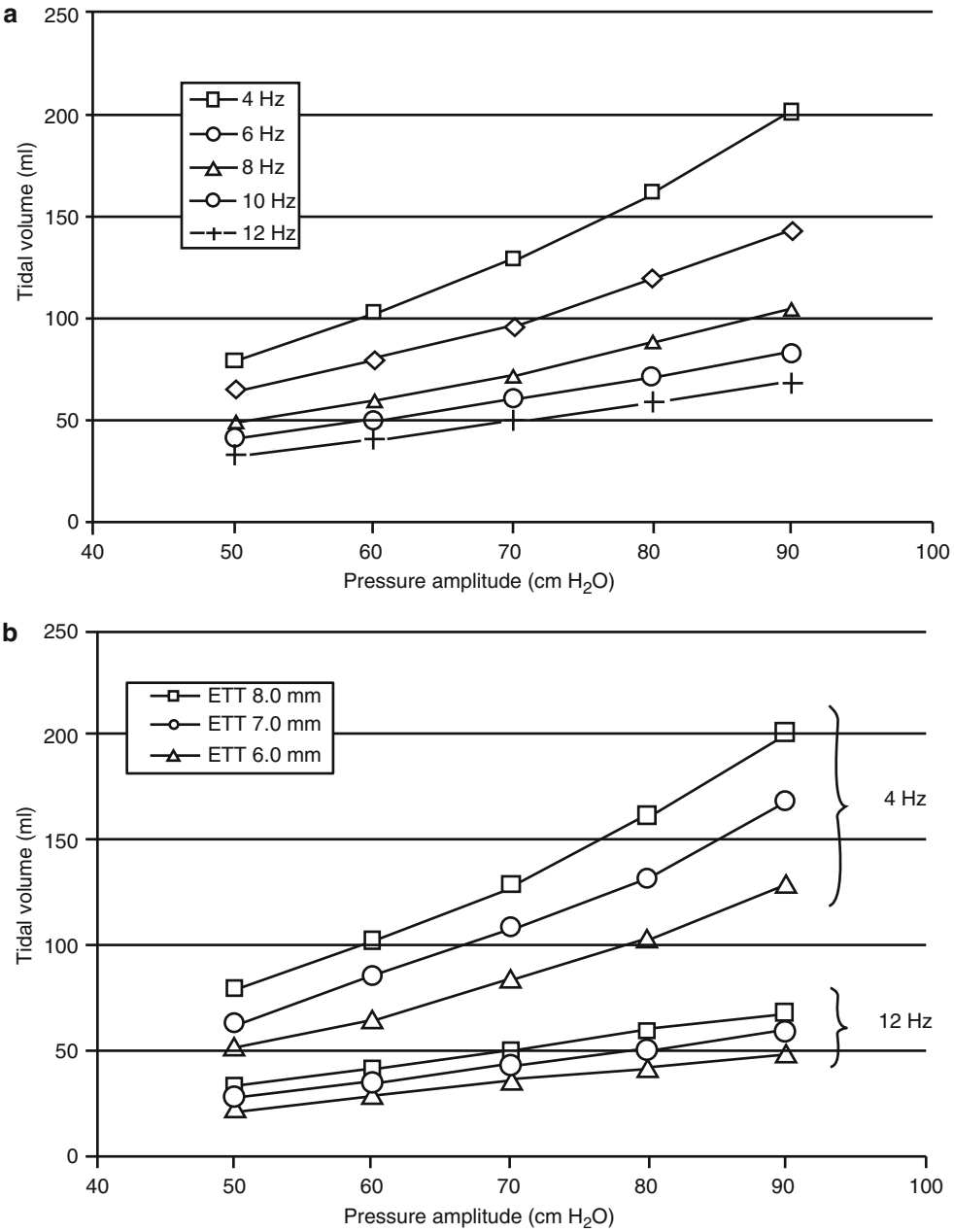

Fig. 10.4 Effect of frequency, amplitude, and ETT diameter on tidal volume delivery during HFOV. Data shown in this figure were collected during ventilation of a test lung (MI Instruments, Grand Rapids, MI) with a 3100B oscillator. In these experiments, bias flow is constant at 30 L/min, compliance is constant at 30 mL/cm H_2O, and I:E is constant at 1:2. Tidal volume is measured using an adult hot wire anemometer. Panel (**a**) depicts the relationship between tidal volume and pressure amplitude at a range of frequencies (4–12 Hz), using an 8 mm (inner diameter) endotracheal tube (*ETT*). Increasing frequency by 2 Hz reduces tidal volume by an average of 21.3 ± 4.1 %. A similar frequency-tidal volume relationship was confirmed by the investigators in a series of adult patients with ARDS, intubated with an 8 mm ETT. In these patients, increasing amplitude by 10 cm H_2O produced an average tidal volume increase of only 5.6 ± 4.5 %. Panel (**b**) depicts the effect of ETT diameter on the relationship between tidal volume and pressure amplitude, at 4 and 12 Hz (Reprinted from Hager et al. [30]. With permission Wolters Kluwer Health)

during conventional ventilation can be delivered when "low frequency HFOV" is used (Fig. 10.4). Small animal models of lung injury appear to confirm that low frequency ventilation (5 Hz) produces histologic evidence of more severe ventilator-associated injury than high frequency ventilation (15 Hz), although studies differ on the magnitude of this difference [45, 46]. In accordance with these data, contemporary HFOV management protocols suggest maintaining the frequency at the highest level that will provide adequate ventilation [30, 43, 44, 47, 48] (Fig. 10.5). For patients with lower airways disease or for small infants who achieve adequate recruitment on low mean airway pressures, some experts advocate modest reductions in maintenance frequency in order to counter the tendency for lower airways collapse and air trapping in these situations [42].

If employing an "*open lung*" ventilation strategy for diffuse alveolar disease (Fig. 10.5), a static recruitment maneuver is performed, and Paw is adjusted relative to the initial setting (in 1–2 cm H_2O increments) until the arterial saturation stabilizes at ≥90 %. The next step in confirming that the patient has achieved a satisfactory degree of alveolar recruitment is to titrate the FiO_2 downward, with the goal of arriving at a Paw that will allow arterial saturations to stabilize at ≥88–90 % (PaO_2 55–80 Torr) using an FiO_2 of ≤0.6, without evidence of hyperinflation or decreased cardiac output. Patients with any degree of intravascular volume depletion

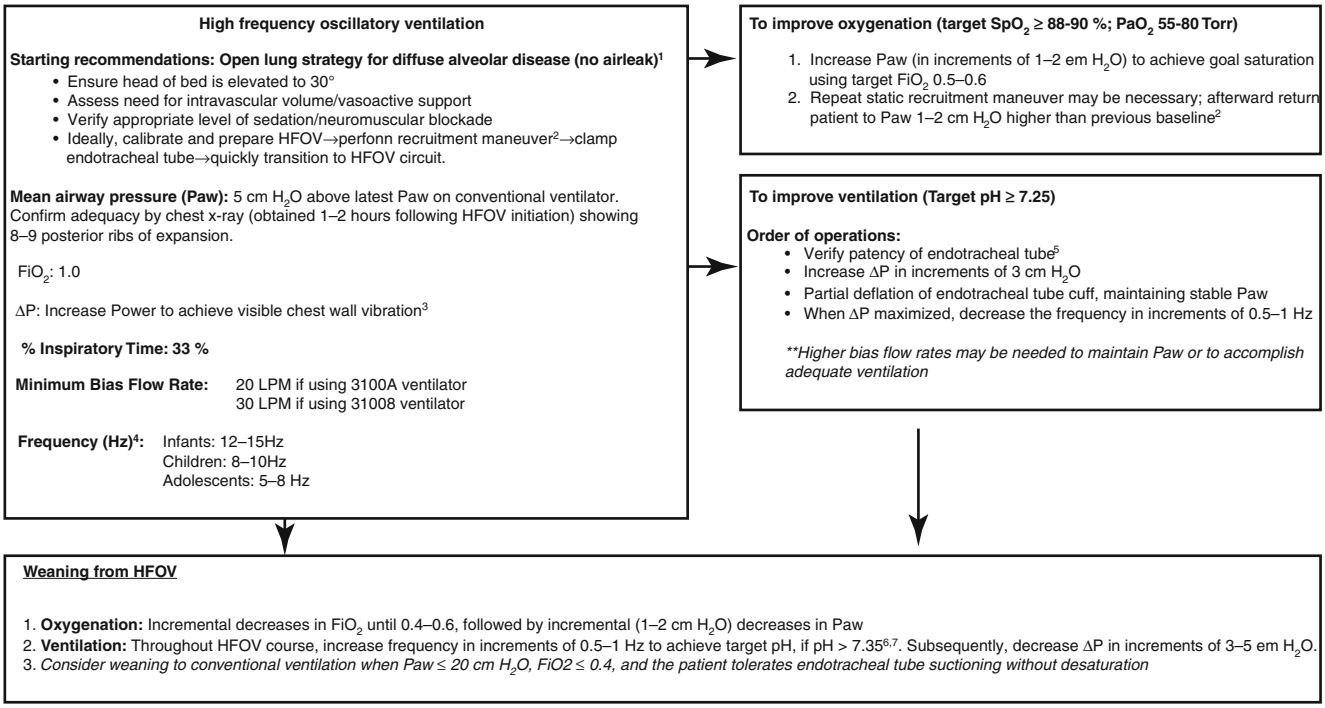

Fig. 10.5 Transitioning the critically ill child from conventional mechanical ventilatory support to HFOV HFOV initiation, maintenance, and weaning parameters. *1* See text for airleak strategy modifications, *2* Recruitment maneuvers can precipitate acute hemodynamic compromise and should not be routinely performed in patients with hypotension or active airleak. Careful hemodynamic monitoring is advised, and recruitment maneuvers should cease if hypotension occurs [44], *3* Magnitude and extent of chest wall vibrations will vary according to chest wall and/or abdominal compartment compliance, *4* To maximize the lung protective effects of HFOV, the maintenance frequency setting should target the upper limit of each age-based range, *5* Suctioning the poorly compliant lung can result in rapid desaturation. Preoxygenation is recommended, *6* This protocol presumes permissive hypercapnea with target pH ≥ 7.25. This approach is not recommended if there are clear contraindications to permissive hypercapnea (e.g., increased intracranial pressure), *7* Increasing frequency can affect oxygenation by reducing the % inspiratory time. Monitor oxygenation carefully as frequency is adjusted upward (Adapted from Ventre and Arnold [130]. With permission from Elsevier)

will often require volume expansion during the recruitment phase of HFOV initiation because under these conditions, alveolar pressure can quickly exceed the perfusing pressure of the adjacent pulmonary vasculature, creating an increase in alveolar dead space and hemodynamic deterioration [49, 50]. The final step in verifying the adequacy of lung recruitment following HFOV initiation, and an important mechanism for monitoring it thereafter, is to ensure that both hemidiaphragms are displaced to the level of the 8th or 9th posterior rib on chest x-ray [19]. When the patient demonstrates an ability to maintain target saturations on FiO_2 of 0.5–0.6 for a period of time, he or she will generally begin to tolerate slow downward titrations of Paw in increments of 1–2 cm H_2O, provided saturations remain stable. Once compliance begins to improve, surface forces will normalize, rendering the lung less prone to closure, and thus allowing lung volume to be maintained as Paw is decreased [51]. Until this occurs, suctioning should be minimized and unnecessary circuit disconnections should be avoided.

A typical sequence of steps for addressing hypercarbia after verifying the patency of the endotracheal tube and an appropriate degree of lung inflation includes (i) increasing the ΔP in increments of 3 cm H_2O until Power is maximized, (ii) subsequently decreasing the frequency in increments of 0.5–1 Hz, and (iii) partially deflating the endotracheal tube cuff, if present, to allow additional egress of CO_2 (Fig. 10.5) [34, 52, 53]. In the latter case, any decrement in Paw should be corrected by further restricting the circuit pressure control valve (turning the "mean pressure adjust" knob clockwise) or by increasing the bias flow of fresh gas as necessary to maintain a stable level of distending pressure [34, 53]. In the event that very high pressure amplitudes are required to provide adequate ventilation, typical maintenance bias flow settings may be inadequate to ensure CO_2 clearance from the circuit. In this setting, the bias flow should be augmented to counter potential increases in the circuit's effective dead space [30, 39].

If employing an HFOV strategy targeted at managing active air leak, the lung is initially recruited using stepwise increases in Paw to achieve an SaO_2 ≥88–90 % (PaO_2 55–80 Torr) using an $FiO_2 \leq 0.6$. Ideally, Paw and ΔP are then slowly lowered to a point just below the "*leak pressure*", the

value at which air is no longer seen draining from the thoracostomy tube, if there is one in place. From this point, hypoxia should be addressed by preferentially increasing FiO_2 to 0.8 before increasing the Paw. In patients with airleak, routine recruitment maneuvers should be avoided following initiation of HFOV, if possible. Ventilation should be provided using the highest frequency that will allow adequate CO_2 clearance, a technique which will minimize both inspiratory time and tidal volume [44]. Maintenance of a controlled modest respiratory acidosis with $pH \geq 7.25$, is preferred unless clear clinical contraindications preclude this approach [23, 54–56]. Once chest radiographs indicate that the airleak has sealed for 24–48 h, many patients will tolerate a transition to a typical HFOV strategy for diffuse alveolar disease, as outlined above.

HFOV in the Neonate and Infant

Neonatal Respiratory Distress Syndrome

High chest wall compliance, surfactant deficiency, and unstable end expiratory lung volume all interact to potentiate repetitive cycles of derecruitment and reinflation that make the preterm neonatal lung particularly well-suited to an open lung strategy of ventilation. Over 20 years ago, a preclinical study exposing surfactant-deficient premature baboons to either HFOV or conventional ventilation demonstrated that early use of HFOV appeared to protect the animals from developing mechanical, biochemical, and histologic evidence of hyaline membrane disease [57]. A follow up study published in 2000 exposed surfactant-deficient premature baboons to exogenous surfactant plus either early HFOV or "lung sparing" conventional ventilation with tidal volumes reduced to 4–6 mL/kg [58]. HFOV was initiated using a Paw 2 cm H_2O above what was required to stabilize the animal on the conventional ventilator. Target blood gas tensions in each group were identical ($PaCO_2$ 45–55 Torr; PaO_2 55–80 Torr), and high supplemental oxygen fractions were avoided through preferential increases in mean airway pressure or PEEP. Remarkably, the animals received supportive care for 1–2 months, allowing the investigators to sequentially examine an array of mechanical, cellular, and biochemical parameters as they sought to determine whether HFOV could mitigate the development of chronic lung disease over time. Animals supported with HFOV demonstrated significantly better pulmonary mechanics for nearly every one of the 8 time points at which they were evaluated between 12 h and 28 days ($p<0.05$). Although between-groups differences for tracheal cytokine concentrations were less consistent across the study period, conventionally ventilated animals demonstrated significantly higher macrophage/monocyte, eosinophil, and lymphocyte infiltration by 10 days ($p<0.05$). Finally, while both groups of animals demonstrated histopathologic findings consistent with chronic lung disease on *post mortem* examination, HFOV supported animals showed significantly better lung inflation patterns by panel of standards analysis ($p<0.001$). Together these studies are representative of a remarkable two decades of scientific inquiry, which established that ventilator-associated injury amplifies the inflammatory response to the primary parenchymal insult experienced by patients with respiratory failure. Thus, the magnitude of acute lung injury, and the incidence and extent of chronic lung injury, are modifiable through the use of more protective ventilation strategies.

Despite HFOV's sound physiologic rationale and the large body of preliminary evidence affirming its potential advantages [2, 6, 7, 29, 59–61], larger scale efforts to evaluate the efficacy of HFOV versus conventional ventilation for human hyaline membrane disease (i.e., neonatal respiratory distress syndrome or RDS) had a disappointing start. The first large randomized, controlled trial in premature infants comparing high-frequency ventilation using a piston oscillator with conventional mechanical ventilation was published during the pre-surfactant era by the *HIFI Study Group* [62]. This crossover trial was designed to evaluate the impact of HFOV 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 h on conventional ventilation for respiratory failure in the first 24 h of life. Infants randomized to receive HFOV were administered a Paw and FiO_2 equal to those administered on conventional ventilation. Infants assigned to the HFOV arm who had not already been tracheally intubated at the time of randomization were supported using an FiO_2 equal to what they received before intubation, and a Paw of 8–10 cm H_2O. In each arm of the trial, hypoxemia was first addressed by increasing the FiO_2, and then by increasing the Paw [62]. Significantly more infants in the HFOV group crossed over to the conventional arm of the trial after they were judged to have failed therapy with the assigned ventilator (26 % vs 17 %; $p=0.01$). All infants were analyzed as part of the study group to which they were assigned. Ultimately 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. Despite the fact that the HIFI investigators made efforts to limit maintenance mean airway pressures and indeed did not incorporate alveolar recruitment into the HFOV strategy, infants in the HFOV arm experienced a significantly higher incidence of airleak (3 % vs 1 %; $p=0.05$). They also experienced a significantly higher incidence of periventricular leukomalacia and high-grade intraventricular hemorrhage, unanticipated developments that contributed to the trial's early closure [3, 62].

A decade later, two large multicenter trials were published in an effort to clarify the role of high-frequency ventilation in the management of the infant respiratory distress syndrome [63, 64]. By this time, many centers had accumulated a great deal of experience using the 3100A high

frequency oscillator in neonates. Each of these trials emphasized alveolar recruitment as part of the HFOV strategy. In their remarkably well-controlled study, Courtney and colleagues randomized 500 preterm infants to receive either conventional ventilation targeting a tidal volume of 5–6 mL per kg body weight, or HFOV using a frequency of 10–15 Hz [63]. Eligible infants were less than 4 h of age, had received one dose of surfactant, and required mechanical ventilation using a mean airway pressure >6 and an $FiO_2 \geq 0.25$. These investigators were able to show that infants randomized to receive high-frequency oscillatory ventilation successfully separated from mechanical ventilation earlier than those assigned to a lung-sparing strategy of conventional ventilation. Those assigned to high-frequency ventilation also demonstrated a significant reduction in the need for supplemental oxygen at 36 weeks postmenstrual age [63]. 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 [63]. In contrast, the companion trial by Johnson and colleagues included healthier patients, used fewer defined protocols, and pursued more aggressive ventilator strategies. In both study arms, Johnson and colleagues targeted a $PaCO_2$ of 34–53 Torr, while Courtney and colleagues allowed more permissive levels of hypercapnea [63]. 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 CO_2 clearance, the frequency was subsequently reduced [64]. Finally, Johnson's group transitioned the majority of study infants to conventional ventilation for weaning after a median time on HFOV of 3 days, a relatively small proportion of the total time on mechanical ventilation [64]. This trial found no difference between groups in its composite primary outcome, death or chronic lung disease at 36 weeks postmenstrual age.

It is important to emphasize that neither of these studies was able to duplicate the findings of the HIFI group with respect to linking the use of HFOV with the development of airleak or brain injury. However, the difference in outcomes between the two trials is intriguing. It is possible that the rigorously controlled conditions in the Courtney study isolate the effect of HFOV with greater clarity. 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 [63]. Johnson's data suggest the number of infants needed to support on HFOV in order to prevent one occurrence of chronic lung disease is 50 [64]. Although the study design used by Johnson and colleagues may better represent actual practice, the outcomes indicate that exposure to aggressive conventional ventilation practices may ultimately counter the benefits of HFOV.

Congenital Diaphragmatic Hernia

Infants with congenital diaphragmatic hernia (CDH) commonly demonstrate complex pulmonary pathophysiology, deriving principally from alveolar and pulmonary vascular hypoplasia [65]. Over 15 years ago, consistent identification of ventilator-induced lung injury on histopathology specimens recovered from CDH patients [66, 67] began to focus attention on the possibility that aggressive ventilator strategies seeking to manipulate pulmonary vascular resistance through hyperventilation actually produce excess morbidity and mortality in this population. The Hospital for Sick Children in Toronto and Children's Hospital Boston published tandem articles in 1997 in which they reviewed their CDH outcomes over a 14 year time span (1981–1994) [66, 67]. In each paper, outcomes were stratified by time periods in which the prevailing management strategy was different than the one that the institution had used before. While overall survival for CDH was similar at each institution, both saw improved survival rates after instituting a strategy of permissive hypercapnea. In Boston, this difference achieved statistical significance (69 % survival vs 44 %; $p = 0.007$) [68]. In Toronto, where clinicians tended to use HFOV more commonly for CDH than their Boston colleagues, the use of HFOV was not independently associated with improved survival [66]. By now a variety of centers have published case series in which infants with CDH demonstrate dramatic short term reductions in $PaCO_2$ and improvements in oxygenation when managed with HFOV [69, 70]. Some of these reports appear to confirm the Toronto experience that the use of HFOV may in fact be associated with an improvement in survival in this population [69–71].

Overall the role of HFOV in the management of infants with CDH is still evolving. For those clinicians who opt to use HFOV for this population, it is essential to recognize that infants with CDH do not have inherently recruitable lungs. In this setting, attempts to improve gas exchange by applying high levels of mean airway pressure can actually increase the dead space fraction and may result in acute inflammatory injury, alveolar or airway rupture, or potentially dangerous elevations in pulmonary vascular resistance. For this reason, experienced centers often recommend limiting the mean airway pressure to 16 cm H_2O or less [72]. The Hospital for Sick Children in Toronto has developed an HFOV protocol that emphasizes maintaining preductal SaO_2 above 85 %, tolerating hypercarbia provided the pH is compensated, and initiation of HFOV when the peak inspiratory pressure on conventional (phasic) ventilation exceeds 25 cm H_2O. This institution has reported significantly increased survival among CDH infants since implementing this set of guidelines in 1995 [72].

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 from a variety of causes. 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 either HFOV alone or conventional ventilation combined with iNO [73]. Crossover as a result of treatment failure resulted in combined therapy with HFOV and iNO. The study found that patients demonstrated significant short-term improvements in PaO_2 during combined treatment with HFOV and iNO, after failing either therapy when it was delivered alone [73]. Combining HFOV and iNO was particularly effective among patients with severe parenchymal disease attributable to RDS and meconium aspiration [73]. The suggestion that iNO efficacy depends upon the adequacy of alveolar recruitment is also supported by a retrospective analysis of data from older children who were enrolled in a multicenter randomized trial of the use of iNO in the treatment of acute hypoxic respiratory failure[74].

Air Leak Syndromes

Given the expectation that satisfactory gas exchange occurs at a lower pressure cost during HFOV, it is not surprising that this therapy has been applied with success in severe air leak syndromes. In one case series, 27 low birth weight infants (mean birthweight 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, FiO_2, and ultimate resolution of air leak. Overall survival among non-septic patients was 80 % [75].

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 due to respiratory syncytial virus [76, 77]. A couple of small case series have reported the successful application of HFOV using an open lung strategy in young infants with bronchiolitis [76, 77]. Applying a relatively high Paw in this clinical context follows the observation that lower Paw may promote worsening hyperinflation by creating *choke points* that impede expiratory flow [42]. The investigators used a frequency of 10–11 Hz and I:E of 0.33, with initial pressure amplitude (ΔP) in the 35–50 cm H_20 range. All patients survived without development of pneumothoraces attributable to HFOV and without need for ECMO [76, 77].

HFOV 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 [55, 78]. In general, each concluded that HFOV may be applied safely as rescue therapy in pediatric patients with severe hypoxic lung injury, and that its use is associated with improvement in physiologic endpoints such as $PaCO_2$ and oxygenation index ($OI = [(Paw \times FiO_2)/PaO_2)] \times 100$). In addition, there were no reports of worsening air leak [55, 78]. Each of these studies initiated HFOV after recruiting the lung, but one of them [55] 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 [54]. 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 ($SaO_2 \geq 90$ % and $FiO_2 < 0.6$), and in patients with air leak, airway pressure was then limited while preferentially increasing in FiO_2 to achieve saturations of ≥85 % and pH ≥7.25 until it resolved [54]. The study found no difference in survival or duration of mechanical ventilatory support between the two groups. However, significantly fewer patients randomized to receive HFOV remained dependent on supplemental oxygen at 30 days, compared to those who were randomized to receive conventional ventilation, despite the use of significantly higher Paw in the HFOV group [54]. The OI, used often in the pediatric literature to quantify oxygenation failure, was shown in this study to discriminate between survivors and non-survivors after 24 h 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 h predicted mortality with an odds ratio of 20.8, sensitivity of 62 %, and specificity of 93 % [54]. *Post hoc* analysis revealed that outcome benefits were not as great among patients that crossed over to the HFOV arm [54], supporting the suggestion by numerous studies that HFOV is most efficacious if employed early in the course of disease, using a strategy that emphasizes alveolar recruitment [13, 57, 78–80].

Other Conditions

Published reports on the use of HFOV for treatment of lower airways disease in older pediatric patients are few. In one interesting case report, HFOV was successfully applied to a toddler with status asthmaticus [81]. 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 h of therapy) without apparent air leak [81]; however, the use of HFOV in obstructive lung diseases must be considered carefully.

HFOV in the Adolescent and Adult

Early experience with the use of HFOV on adolescent and adult patients with hypoxic respiratory failure is summarized in several case series [34, 82]. In each, low frequency (maximum 5–6 Hz) HFOV using a strategy of volume recruitment was used as rescue therapy in 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 [34, 82]. 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 [34, 82]. Non-survivors 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.

The first multicenter prospective, randomized controlled trial designed to evaluate the safety and efficacy of HFOV as compared to conventional ventilation in the management of early ARDS ($PaO_2/FiO_2 \leq 200$ while on PEEP 10 cm H_2O) in adult patients was published in 2002 [53]. 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 a pressure-limited 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 %. After the transition, conventional ventilation was reinstituted using a Paw equivalent to the last setting on HFOV [53]. With regard to short-term physiologic measures, these investigators also reported a significantly higher Paw and significant early increases in PaO_2/FiO_2 among patients on HFOV [53]. 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 in OI over the first 72 h of the study period, while non-survivors did not [53]. Although the OI is not a measure traditionally reported in the adult literature, it has been reported by some investigators as predictive of mortality in adult ARDS [82]. This trial 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 %) [53].

Since the publication of that first clinical trial, experience with adult HFOV has been documented in six subsequent randomized controlled trials comparing HFOV to conventional ventilation in patients with acute hypoxic respiratory failure [83–88]. The largest of these enrolled 61 patients [85]. All of these studies maintained HFOV at a frequency of 5 Hz or less, a practice now believed to generate tidal volumes approaching what would be delivered during conventional ventilation [44, 89]. In 2007, Fessler and colleagues issued a consensus document in 2007 recommending that HFOV protocols for adult ARDS combine high amplitudes with the highest oscillatory frequency that will produce a target pH of 7.25–7.35 (Fig. 10.5) [44]. The large-scale, multicenter **Oscil**lation for **A**RDS **T**reated **E**arly ("OSCILLATE") trial was the first to prospectively test this approach [90]. This trial was designed to evaluate the impact of high-amplitude, maximal frequency HFOV against an "open lung", low tidal volume conventional ventilation strategy on all-cause hospital mortality for adults with ARDS. The investigators randomized 548 adults ≥16 years of age with acute hypoxic respiratory failure (PaO_2/FiO_2 ≤200 on standardized ventilator settings) and diffuse alveolar disease to receive either phasic ventilation targeting a tidal volume of 6 mL/kg and plateau pressure ≤35 cm H_2O -or HFOV using the Sensormedics 3100B (CareFusion Corporation, Yorba Linda CA), oscillating at the highest possible frequency that would allow maintenance of an arterial pH >7.25. Both ventilator protocols targeted a PaO_2 55–80 Torr, guided by a standardized PEEP (or Paw)-FiO_2 grid, and both included recruitment maneuvers. Transition from HFOV to phasic ventilation and weaning from mechanical ventilatory support

were strictly protocolized. Ultimately the steering committee terminated the OSCILLATE trial well short of its goal of enrolling 1,200 patients, after three consecutive interim analyses suggested an increase in mortality with HFOV. In the final analysis, the HFOV group had an in-hospital mortality of 47 % compared to 35 % in the control group (RR for death with HFOV 1.33; 95 % CI 1.09–1.64, p = 0.005). This new and perhaps surprising development in the history of HFOV trials has several intriguing implications. As the OSCILLATE trial investigators suggest, it is possible that the theoretical benefits of maximal frequency (i.e., "low stretch") HFOV may be countered by deleterious effects from the high mean airway pressures that are typically required when using such a strategy [90]. The OSCILLATE trial outcomes may also compel clinicians to consider the possibility that HFOV may be a technique better suited to patients with diffuse alveolar disease and increased chest wall compliance—conditions that often coexist in infants and young children with acute lung injury and ARDS.

Adjuncts to HFOV: Non-invasive 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, AP 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. The operator must often use intuition when adjusting ventilator settings, risking sudden and clinically significant de-recruitment or alveolar over-distension. 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 non-invasively at the bedside of patients receiving 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 zig-zag distribution along their circumference are applied to the patient. One is typically placed around the chest, 3 cm above the xyphoid 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 [91, 92]. 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[91]. In 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 [92]. Experience with RIP in human subjects is limited to investigations of its application during conventional ventilation. One study in adult patients [93] and another in pediatric patients [94] have utilized RIP to quantify the relative degree of de-recruitment that is associated with closed, *in-line* techniques for endotracheal tube suctioning, as compared to 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 has revealed about the heterogeneity of parenchymal involvement in ARDS [95] will ultimately depend on developing non-invasive bedside technologies that are capable of identifying regional changes in lung volume and pulmonary mechanics. CT 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 [95, 96] (Figs. 10.1 and 10.6). 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 over-distension 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 which 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, while fluid and solid phases (including atelectatic or consolidated lung) would be associated with lower impedance [97]. The impedance values that are generated are referenced to a baseline measurement, and represent relative rather than absolute changes in electrical properties [96]. This process creates a tomogram that depicts the distribution of tissue electrical properties in a cross-sectional image (Fig. 10.7), and the thickness of the slice of thorax that is represented in

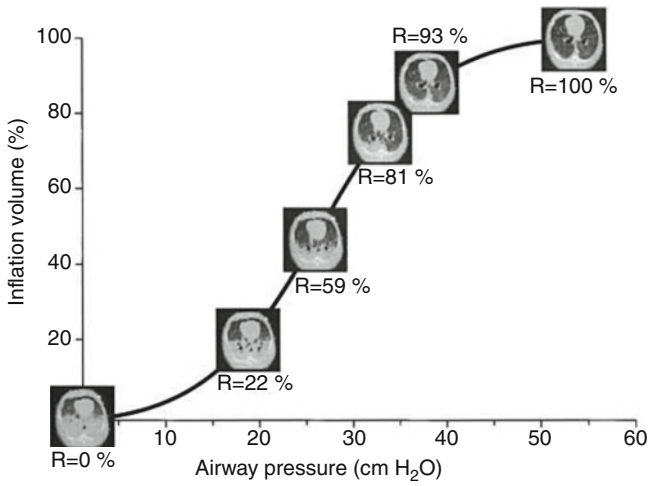

Fig. 10.6 Alveolar recruitment along the pressure-volume curve in ARDS: Data shown are from a large animal, oleic acid lung injury model. As lung volume increases toward total lung capacity, aeration of dependent lung units increases substantially, but at a very high airway pressure cost. At high airway pressures, non-dependent lung units may be vulnerable to overdistension. "*R*" indicates the percentage of total lung recruitment at each corresponding airway pressure (Reprinted with permission of the American Thoracic Society. Copyright (c) 2013 American Thoracic Society. Gattinoni et al. [95]. Official Journal of the American Thoracic Society)

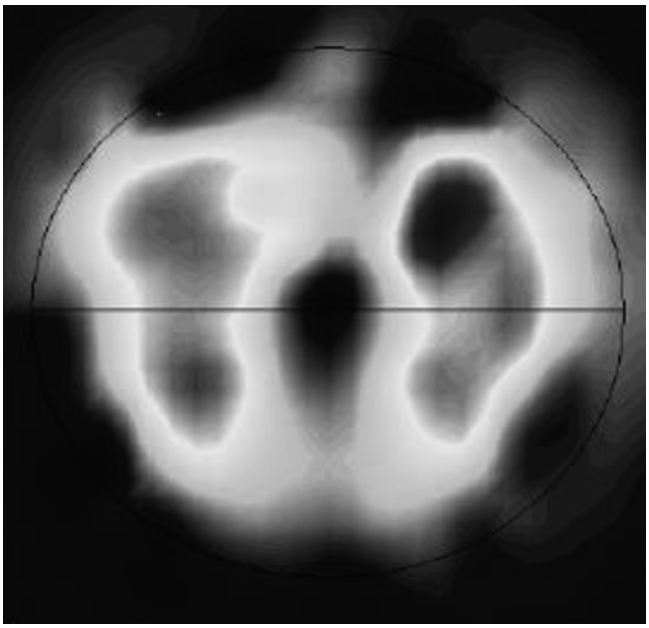

Fig. 10.7 EIT image of the lung. The orientation is the same as for a CT image. Both lung fields show equal impedance change during spontaneous breathing (Adapted from Wolf and Arnold [96]. With permission from Springer Science + Business Media)

the image varies between approximately 15 and 20 cm, depending on the circumference of the chest [96, 98]. 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 it is also capable of dynamic measurements at low lung volumes [96, 99]. This system scans at a rate of 13–44 scans/s (Hz), generating up to 44 cross-sectional images per second [96].

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 [96, 100], and have demonstrated good correlation between EIT-derived regional changes in lung impedance and CT-derived regional variations in aeration [96, 101]. 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 compared with pressure-volume curves that are obtained using a supersyringe method, suggesting that recruitment is more uniformly distributed between dependent and non-dependent areas during HFOV [102]. 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 [103]. A group of investigators at Children's Hospital Boston recently 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 (Fig. 10.8) [104] . The same investigators went on to correlate regional impedance changes with regional overdistension during HFOV in an animal model of acute lung injury, a finding bringing EIT research a step closer to identifying a precise role for this technology in the management of patients on HFOV [105].

It is tempting to expect that EIT will soon facilitate the development of more 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 [97]. This phenomenon may account in large part for the variation between EIT measures of regional lung impedance and CT measures of regional lung density [103]. In addition, because EIT

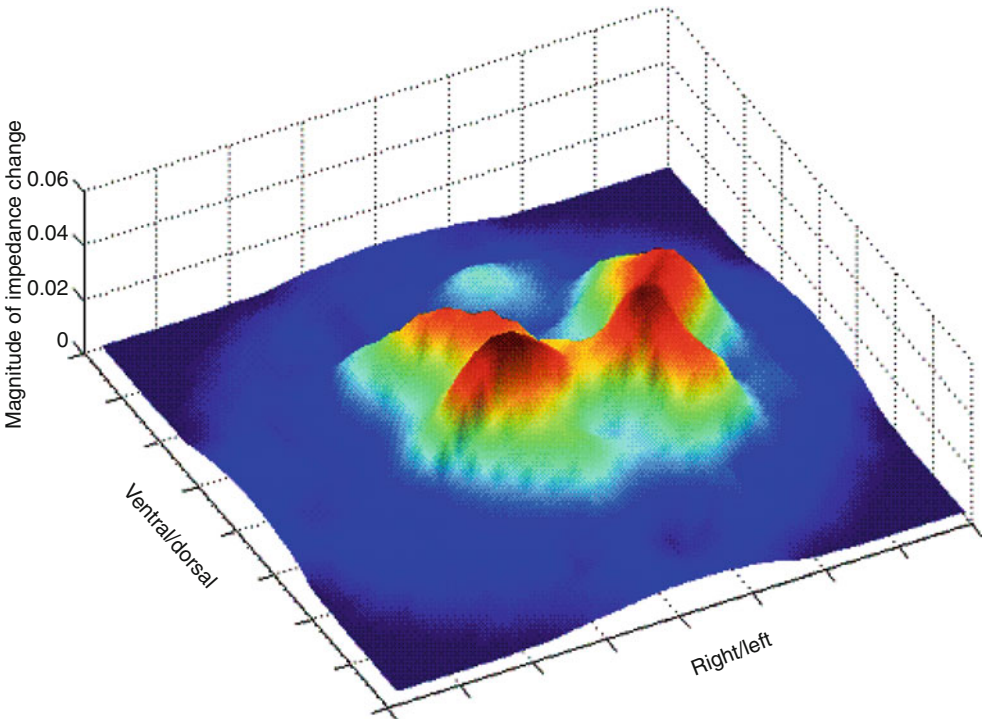

Fig. 10.8 Three dimensional depiction of recruitment after suctioning on HFOV. The standard deviation of impedance change after reconnection to the ventilator is displayed (Reprinted from Wolf and Arnold [104]. With permission from Wolter Kluwers Health)

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 [106] and extravascular lung water [107]. 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 from HFOV

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 initiated 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 [63, 64, 79], but this is difficult to accomplish in the older pediatric and adult patient, who may be less likely to tolerate a plane 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 $\leq$20 cm H_2O, FiO_2 is reduced to $\leq$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 [23]. 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.

Other Developments: Revisiting High Frequency Percussive Ventilation

Since the mid 1980s, reports have occasionally appeared in the literature examining the role of high frequency percussive ventilation (HFPV) in the management of neonates, children, and adults with lung injury from a variety of causes. HFPV is a form of high frequency ventilation in which a single ventilator (Percussionaire Corporation, Sandpoint ID) coordinates the set parameters of both conventional ventilation and HFOV

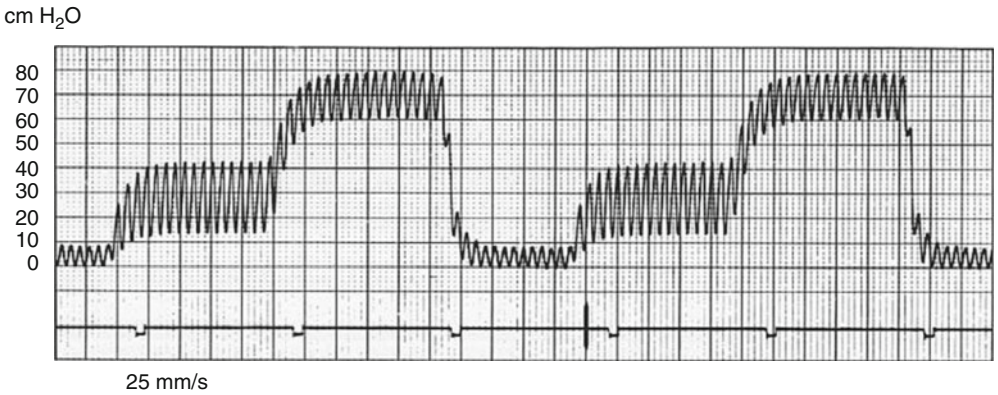

Fig. 10.9 Pressure-time waveform during HFPV ("convective pressure rise" feature engaged): stepwise progression to end inspiratory pressure is depicted. At the beginning of inspiration, oscillatory pressures reach an initial plateau. A "convective pressure rise" carries the breath toward the peak equilibrium pressure, which is then released at the end of inspiration toward the baseline PEEP (CPAP). In this tracing, oscillations are activated during both the inspiratory and the expiratory phase (From The VDR-4 Manual of Understanding [109], used with permission granted by Dr. Forrest Bird)

to deliver time-cycled, oscillatory, subphysiologic tidal volumes at approximately 3 Hz to at least 15 Hz. These are superimposed on time-cycled, pressure-limited tidal volumes (10–15/min) whose magnitude is determined by peak inspiratory pressure (PIP) and PEEP (CPAP) [108]. Oscillations during HFPV are created by a pneumatic "Phasitron®" (piston) positioned near the airway opening, which acts as both an inspiratory and expiratory valve and generates progressive, accumulative high velocity percussive waves that conduct into the lung. The net effect is a multiphasic oscillatory pattern that hits its maximum pressure during inspiration and its minimum pressure during expiration, when the lung recoils to the set PEEP (CPAP) level (Fig. 10.9) [108, 109]. The overall architecture of the respiratory cycle during HFPV is perhaps responsible for the observation that many patients can tolerate it without the need for neuromuscular blockade [108, 110]. During HFPV, the operator controls PIP, PEEP (CPAP), inspiratory time, expiratory time, percussive rate, and "conventional" rate [108].

Proponents of HFPV contend that it enhances tidal convective CO_2 clearance while augmenting oxygen diffusion through high velocity flow, in the manner common to all high frequency techniques [108, 109]. In addition, percussive waves are believed to promote the clearance of airway secretions and debris, a process that is further potentiated by periodic lung recoil [108, 111]. This is the rationale underlying the use of HFPV in patients with inhalational lung injury, although published studies examining the impact of HFPV on the incidence of pulmonary infection have shown conflicting results [112–115]. A variety of reports ranging from small case series [116–123] to case control studies [112, 113] and small-scale prospective randomized trials [114–116, 124–128], have documented improved CO_2 clearance and oxygenation efficiency at lower PIPs, when comparing HFPV to "traditional", high tidal volume conventional ventilation in neonates, children, and adults. There is a single published trial examining the efficacy of HFPV relative to lung protective ventilation using a modified version of the ARDSnet protocol [16, 115]. The incidence of ventilator-associated pneumonia, diagnosed by contemporary consensus criteria, was examined as a secondary outcome measure in this trial. The investigators randomized 62 burned adult patients with acute respiratory failure to either HFPV or conventional ventilation using tidal volumes of 6 mL/kg predicted body weight and plateau pressure limitation to ≤30 cm H_2O. Only a portion (37 %) of the study population had documented inhalational injury. In the HFPV cohort, the investigators reported significant reductions in PIP up to 5 days following randomization. However, this did not translate to an overall difference in the study's primary outcome measure, ventilator-free days in the first 28 days of the trial [115]. Significantly more patients in the conventional ventilation arm of this trial experienced new airleak or otherwise unexplained pneumatocele (13 % vs 0 %; $p=0.04$). There was a trend toward reduced incidence of ventilator-associated pneumonia in the HFPV arm, but this difference did not achieve statistical significance (32 % vs 52 % $p=0.12$). There was no difference in plasma cytokine levels between study groups. Significantly more patients in the conventional ventilation arm required a rescue mode of ventilation for failure to meet predetermined ventilation and/or oxygenation goals (29 % vs 6 %; $p=0.02$), a finding which closed the trial short of its goal of enrolling 170 patients. Thus, the available evidence suggests that HFPV is associated with short-term improvements in the efficiency of gas exchange among lung injured patients, but clinical trials have not yet confirmed a clear advantage of this modality over current best practices for either conventional ventilation or HFOV. In particular, the impact of the larger, low frequency tidal volumes on the inflammatory response and overall course of lung injured

patients managed with HFPV has yet to be fully elucidated [110]. Additional study will be needed before more widespread use of this modality outside of a controlled investigational setting would be justified.

Conclusions

In spite of 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 in 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.

HFOV 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 ventilator-induced lung injury [8, 10–13] 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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