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Review Article

High Frequency Oscillatory Ventilation

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Introduction

Mechanical ventilation can induce lung injury, particularly in premature and diseased lungs. There is increasing evidence that high peak inspiratory pressures and repetitive end-expiratory collapse are major determinants of lung injury. Efforts to minimize ventilator-induced lung injury in infants with Respiratory Distress Syndrome (RDS) have focused on the potential role of High-Frequency Oscillatory Ventilation (HFOV) which has been studied in newborn infants with RDS. High-frequency ventilation is a method of ventilation in which alveolar gas exchange is maintained by pressure swings initiating small displacements of ventilator gases, considerably smaller than conventional tidal volumes, at frequencies, generally from 5-20 Hz. High frequency ventilation allows higher end-expiratory pressures with lower peak inspiratory pressures and higher mean airway pressures and is therefore proposed as currently the most optimal form of lung protective ventilation.

There are clinical and animal data indicating that HFOV is a lung-protective ventilator strategy, in the setting of neonatal respiratory failure, if lung volume recruitment is carried out. However, substantial controversy remains about when and how HFOV should be used. A minority of clinicians who use HFOV as a primary mode of ventilation for infants who require ventilator support. At the other extreme are those who view it as a rescue technique, only to be used when conventional ventilation has failed or in an early rescue manner in infants judged to be at high risk for complications from conventional ventilation.

Mechanisms of Gas Transport

One of the fundamental principles underlying the increased efficiency of HFOV is the altered dynamics of gas flow distribution, challenging the traditional concepts of gas transport during conventional ventilation. A number of different mechanisms have been identified as having a contributory role in promoting gas exchange during HFOV, including bulk convection, asymmetric velocity profiles, pendelluft, cardiogenic mixing, Taylor dispersion and turbulence, molecular diffusion, and collateral ventilation. It is likely that they are not mutually exclusive and that a combination of the mechanisms augments gas transport during HFOV.

The following mechanism should be mentioned:

Bulk convection

Unlike conventional ventilation, bulk convection plays a relatively small role in gas transport during HFOV, although it is likely to contribute significantly to ventilator exchange in the most proximal gas exchange units. In an anesthetized dog model, [1] the decreasing delivered volume to a level below the HFO-circuit-related rebreathing volume causes a sudden rise in the $PaCO_2$. These findings suggest that the efficiency of CO_2 elimination is critically dependent on the net oscillatory volume and that bulk convection has an essential role during HFOV.

Pendeluft

At high frequency, distribution becomes strongly influences by time-constant inequalities, and gas from fast units will empty into slow units. Pressure phase differences can be observed during HFOV, and these differences set up circulating currents, which can interchange gas between neighboring area, homogenizing peripheral gas concentrations.

Collateral ventilation occurring through no airway connections between neighboring alveoli has also been proposed as an additional mechanism of gas transport during both conventional and HFOV. The relatively high resistance of the collateral channels to gas flow is likely to limit the extent to which this mechanism contributes to gas mixing during HFOV [2].

Asymmetric velocity profiles

Asymmetric velocity profiles result in net convective transport of material. Although the more central particles are propelled down the length of the airway, the peripheral particles diffuse in radial directions, promoting axial gas exchange with the expired alveolar gas [3]. This phenomenon is particularly evident at the airway bifurcations where there is skewing of the inspiratory profile compared with a more symmetric expiratory velocity profile. The airway bifurcation phenomenon streams fresh gas toward the alveoli along the inner airway walls while "alveolar" gas is streamed away from the alveoli along the outer wall, and hence plays an important role in the longitudinal convective transport mechanisms during HFOV.

Taylor dispersion

The longitudinal dispersion of tracer molecules in a diffusive process is augmented by radial transport mechanisms, when laminar flow is applied in both the absence or presence of turbulent eddies and secondary swirling motions [4]. The combination of Taylor dispersion and molecular diffusion (augmented dispersion) accounts for almost all gas transport during HFOV [5]. Time-constant inequalities and phase lags between lung regions may set up bulk convective currents recirculating air between neighboring lung units [6,7]. Exchange during HFOV may be improved by the interaction of flow between asynchronous neighboring airways and has been graphically illustrated with stroboscopic filming techniques [8]. Asymmetries in inertance and compliance of peripheral airways and lung units are more important determinants of pendelluft than are asymmetries in resistance [9].

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Cardiogenic mixing

The superimposition of the rhythmic, strong contractions of the heart may further promote peripheral gas mixing by promoting the generation of flow within neighboring parenchymal regions rather than at the airway opening. The contribution of cardiogenic oscillation during HFOV has been suggested that cardiogenic mixing may account for up to half of the oxygen uptake in the presence of totally apneic respiration. Collateral ventilation occurring through non-airway connections between neighboring alveoli has also been proposed as an additional mechanism of gas transport during both conventional and HFOV [10].

Molecule diffusion

Spontaneous mixing of gas particles arising from Brownian motion contributes to the diffusion of gases in the respiratory tract. Gas velocities approximate zero in the alveolar region as a result of the very high total cross-sectional area. The dominant mechanism for gas mixing in this zone is molecular diffusion, with net transport of gas best described by Fick's law.

It is likely that a combination of the mechanisms augments gas transport during HFOV [11].

Gas Exchange during HFOV

Oxygenation

During HFOV, oxygenations is decoupled from CO_2 elimination in that changes made to alter oxygenation have little effect on CO_2 elimination from the lungs and conversely, changes made to effect $PaCO_2$ change have little effect on oxygenation. To change oxygenation, lung volume has to be adjusted, as there is a close relationship between lung volume and surface area for gas exchange. Because during HFOV, lung volume is established with MAP, the MAP adjustment will have a profound effect on oxygenation.

Mean airway pressure and lung volume

Usage of positive Mean Airway Pressure (MAP) during HFOV effectively opens the distal airways, and maintains recruitment throughout the ventilator cycle. A critical procedure in HFOV is the adjustment of MAP to a level that allows optimal gas exchange without overstretching (or collapsing) the lung tissue. If such over distension is not avoided, cardiopulmonary function may be adversely affected and airway leaks may result. High frequency oscillatory ventilation potentially offers the ideal combination of minimum tidal volume while maintaining maximal recruitment, provided sufficient end-expiratory lung volume (during HFOV, PEEP=MAP) is maintained. Moreover, avoids repetitive recruitment and de-recruitment of the unstable lung alveoli, thus preventing end-expiratory collapse. Presently, MAP is adjusted by trial and error or by clinical experience of the user (Figure 1).

The Mean Airway Pressure (MAP) is the CPAP around which the pressure oscillates. When conventional ventilation is superimposed, MAP also depends on PIP and the rate of conventional ventilation. Increasing the MAP along the pressure volume curve will result in increasing lung volume. When lung volume increases above the critical opening pressure (lower inflection point of the lung), lung compliance will improve. Over time, lung compliance continues to improve and when not compensated for by decreased MAP, will result in increasing lung volume and eventually, over distension. This may cause compression of the alveolar vascular bed and increase vascular resistance, decreased preload and cardiac output. Lung over distension can be assessed using chest radiography (flattened diaphragm and/or bulging in the intercostal space).

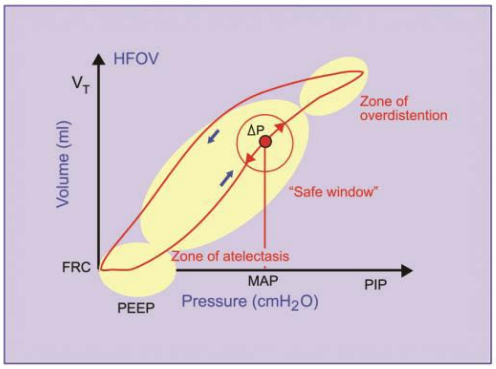

Figure 1: High frequency oscillatory ventilation potentially offers the ideal combination of minimum tidal volume while maintaining maximal recruitment, provided sufficient end-expiratory lung volume (during HFOV, PEEP = MAP) is maintained. Moreover, avoids repetitive recruitment and de-recruitment of the unstable lung alveoli, thus preventing end-expiratory collapse. The Mean Airway Pressure (MAP) is the CPAP around which the pressure oscillates. When "optimum lung volume strategy" is applied during HFOV, the lung volume is kept above the critical closing pressure of the lung throughout the respiratory cycle, the alveolar gas exchange area is enlarged and the time for gas exchange is prolonged.

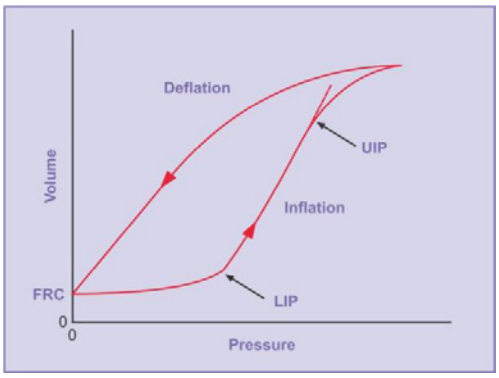

Figure 2: Pressure-volume curve. FRC=functional residual capacity; LIP=lower inflection point; UIP=upper inflection point.
As airway pressure is increased from Functional Residual Capacity (FRC), an abrupt change in the lung compliance is often evident, particularly in injured or surfactant deficient lungs. The Lower Inflection Point (LIP) of the pressure-volume curve may represent the approximate pressure (volume) at which lung units are recruited. The Upper Inflection Point (UIP) at which lung compliance decreases at higher airway pressure was thought to reflect the point at which alveoli are becoming over distended, and therefore potentially damaged.

The introduction of HFOV shortly after birth is beneficial to attain optimal lung volume strategy, using a high MAP before significant lung injury has occurred. Even brief periods of tidal volume ventilation may inflict damage to the lung. In preterm infants with RDS this opening pressure is approximately 10-12 cm H_2O. The physiologic effect of such continuously applied pressure is the opening of atelectasis lung units, resulting in recruitment of lung volume. Opening atelectasis units reduces ventilation-perfusion mismatch

and thus intrapulmonary shunting. Therefore MAP is the crucial parameter to control oxygenation. Lung volume on HFOV remains constant. Recruitment of lung volume can be obtained by increasing the MAP to inflate the lung beyond the critical opening pressure (lower inflection point) at which atelectasis lung units begin to inflate. Inflation is maintained above the closing pressure of the alveoli and airways. When lung volume is recruited and maintained throughout the ventilator cycle V/Q matching is improved. During CMV the alveolar gas exchange area is small and the time for gas exchange is short. When "optimum lung volume strategy" is applied during HFOV, the lung volume is kept above the critical closing pressure of the lung throughout the respiratory cycle, the alveolar gas exchange area is enlarged and the time for gas exchange is prolonged. These can significantly improve oxygenation. Optimal lung volume should be associated with optimizing pulmonary blood flow. This is attained when pulmonary vascular resistance is decreased and cardiac output is not compromised. It has been shown that there is a correlation between lung volume and pulmonary resistance. Expansion of the lungs contributes to pulmonary vasodilatation. At low lung volume, alveoli collapse due to the loss of interstitial traction. This will result in decreased functional residual capacity, decreased alveolar stability and hypoxemia. Additionally, pulmonary vascular resistance increases due to a decreased cross-sectional area of the extra-alveolar vessels. As the lung increases from low to optimal volume, the radial traction to the wall of the large extra-alveolar vessels increases resulting in an increase in cross-sectional area and a reduction in vascular resistance. If the lung becomes over distended, there is increased alveolar compression of the alveolar vessels resulting in increased vascular resistance. Thus at both underinflated and overinflated lung volumes, pulmonary vascular resistance may increase, but vascular resistance is minimized at optimum lung volume. Changes in arterial oxygenation reflect V/Q match.

Optimum lung volume strategy

The pressure-volume curve is often used to illustrate the balance between over distension and recruitment. As airway pressure is increased from Functional Residual Capacity (FRC), an abrupt change in the lung compliance is often evident, particularly in injured or surfactant deficient lungs. The Lower Inflection Point (LIP) of the pressure-volume curve may represent the approximate pressure (volume) at which lung units are recruited. The Upper Inflection Point (UIP) at which lung compliance decreases at higher airway pressure was thought to reflect the point at which alveoli are becoming over distended, and therefore potentially damaged (Figure 2).

When considering the variables that can be adjusted during HFOV (inspiratory time, MAP, peak inspiratory pressure, volume limit, pressure limit), it may appear that defining a "lung protective strategy" for the neonate is extremely difficult. Cyclic opening and closing (recruitment-DE recruitment) of small airways/lung units may lead to increased local shear stress (atelectrauma). The use of adequate MAP is considered as sufficient to prevent DE recruitment and over distension. However, the explanation of ventilator induced lung injury according to the pressure-volume curve is a gross simplification, since recruitment is not complete at the LIP and continues at higher inflating pressures. Similarly, the UIP does not necessarily reflect the onset of over distension. Instead, it may represent the point at which recruitment is complete and therefore

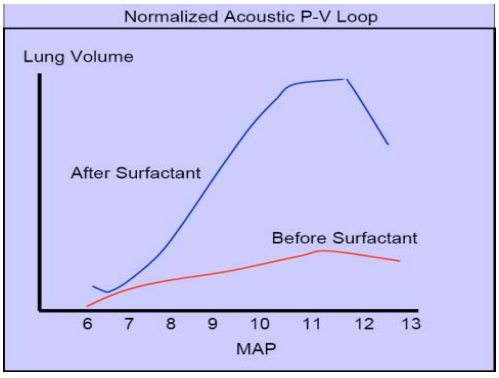

Figure 3: A 32 weeks gestation infant ventilated by HFOV for RDS, a compliance curve was determined by acoustic reflection technique prior to surfactant replacement and shortly after surfactant replacement (Modified from Luria et al IEEE Engineering Med Biol Soc. 2007).

compliance decreases. Furthermore, inflation may be expanding alveoli without necessarily over distending them. The damaged lung in the clinical setting is not homogeneously affected. Applied airway pressure that may be ideal to recruit and ventilate some lung units may be inadequate to open the most densely atelectasis regions, and yet simultaneously cause over distension in the most compliant areas.

In the early stages of uncomplicated RDS, hypoxemia is the result of V/Q mismatch and is readily corrected when optimal lung expansion is reached. In such patients the adequacy of oxygenation is an excellent guide to the need for MAP (Figure 3). This strategy consists of progressive increases in mean airway pressure until adequate oxygenation occurs and FIO_2 less than 0.30 is reached. Changes in MAP should be guided by chest radiographs. The magnitude of mean airway pressure adjustment should be proportional to the degree of under inflation or over inflation as assessed on chest radiographs. At the lower portion of the lung inflation curve, relatively small changes in mean airway pressure can result in significant changes in lung inflation. If a small change in MAP results in a significant increase in FIO_2, a chest radiograph should be obtained to evaluate lung inflation. It is important to recognize that once atelectasis occurs as a result of excessive decrease of MAP, it becomes necessary to re-expand the lungs by a volume recruitment maneuver. The MAP must be transiently increased at least 2 to 3 cm H_2O above the previous setting. This is because the critical opening pressure must be reached before recruitment occurs.

Inspired oxygen fraction

Results of recent animal studies [12,13] indicate that mechanical ventilation with air had little or no effect on lung development genes (VEGF-A, its receptor VEGF-R2, and tenascin C), as compare to ventilation with 40% oxygen. Moreover, 24-hour studies of mechanical ventilation with 40% oxygen showed significant reductions in lung abundance of proteins that affect the formation of alveoli and lung capillaries. These results indicate that mechanical ventilation with oxygen-rich gas at a critical stage of development reduces lung expression of genes that regulate alveolar siltation and angiogenesis. Additionally, mechanical ventilation with 40% oxygen increases pulmonary expression of genes that play a key role in synthesis and assembly of elastic fibers, which can affect the structural

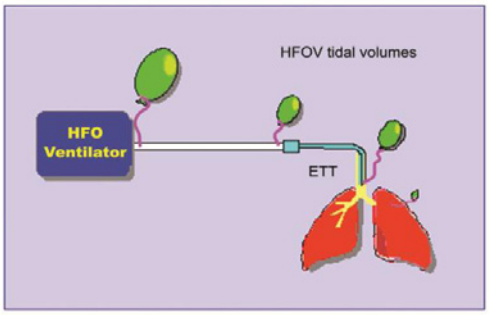

Figure 4: During HFOV there is a relationship between the pressure amplitude (VT) measured at the top of the end tracheal tube and the pressure amplitude that is delivered to the alveoli. Increasing the frequency of HFOV, decreases the amplitude of the pressure wave (tidal volume) at the alveoli, and reduces CO_2 elimination.

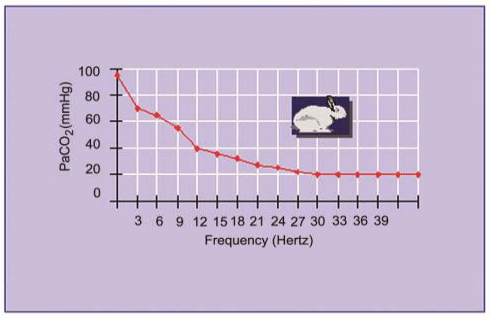

Figure 5: CO_2 transport during HFOV has been shown to directly relate to the oscillation frequency and tidal volume through a power law where the exponents of both frequency and tidal volume are positive.

stability and dispensability of the lung and its vasculature. Thus the importance of determining the fraction of FIO_2 during HFOV is to allow oxygenation while avoiding lung injury. Exposure to a high FIO_2 leads to lung damage.

Co_2 elimination

The relationship between ventilation (CO_2 elimination) and ventilator settings is more complex for HFOV than it is for conventional ventilation.

An important difference between HFOV devices and conventional ventilators is the relationship between the pressure amplitude measured at the top of the endotracheal tube and the pressure amplitude that is delivered to the alveoli (Figure 4). With conventional ventilators operating at relatively low frequencies (<60 breaths per minute), gas exchange occurs almost entirely by bulk flow (convection). In this condition, pressure applied at the airway opening is fully transmitted from the upper airway to the alveoli. As rates increase (75 to 150 breaths minute), however, with a proportional decrease in inspiratory and expiratory time, there is insufficient time within the respiratory cycle for the pressure to equilibrate fully between the upper airway and the alveoli. This is the mechanism for the gas trapping or inadvertent PEEP, which is seen at high rates with conventional ventilation. With HFOV, this attenuation of the pressure amplitude between the upper airway and the alveoli becomes extreme. Gas exchange occurs predominantly by augmented diffusion and the pressure amplitude or volume delivered to the alveoli is significantly less than the amplitude measured at the airway opening. As frequency increases, this attenuation of transmitted pressure becomes more pronounced. This is the reason that increasing the frequency of HFOV, with a concomitant decreases in inspiratory and expiratory time, decreases the amplitude of the pressure wave at the alveoli, and reduces CO_2 elimination.

It has been shown [14] that CO_2 control could be achieved by any combination of tidal volume and frequency. Studies in both theoretical models [5] and in healthy animals and humans [15,16] have demonstrated that Tidal Volume (VT) has a greater effect on gas exchange than frequency (f) during HFOV. As such, ventilation efficiency during HFOV (Q) may be expressed as:

$$Q = f^{a^*}VT^b$$

Where b >a

The values for a and b in this equation approximate 1 and 2, respectively, although the absolute values may be influenced by other factors such as the shape and complexity of the oscillatory pressure waveform. The more dominant contribution of VT to ventilation during HFOV is the result of the oscillatory redistribution of gas from central to distal regions where molecular diffusion overcomes Taylor dispersion as the principal influence on gas transport [17]. It has been shown that HFOV gas transport mechanisms come into play, when VT still exceeds airway dead space volume (VD) [18] and that the transition frequency occurs when alveolar ventilation/ frequency is equal to 20% of VD and VT is equal to 120% VD. The transition frequency refers as frequency marking the transition from conventional to high-frequency gas transport mechanisms, varies in proportion to the ratio of metabolic rate to dead space [19].

Oscillatory volume

The oscillatory volume (VT), which results from the pressure swings (pressure amplitude), determines the effectiveness of this type of ventilation. In the end, ventilation does not depend on the pressure amplitude but on the oscillatory volume, which exponentially affect CO_2 elimination from the lungs. The oscillatory volume depend on the oscillatory frequency (lower frequencies allow high volume and vice versa), resistance and compliance of the respiratory system, the use of different ventilator circuits or ETTs and thus the effectiveness of HFOV.

Oscillatory frequency

During conventional mechanical ventilation, it is important to choose a frequency that achieves optimal gas exchange without air trapping. The optimal range of frequencies is dependent on the patient's intrinsic lung mechanics. The most important aspect of lung mechanics in determining optimal frequency is the time constant τ, which equals the product of dynamic compliance and airway resistance (C^*R). Infants with short time constants can be ventilated effectively at higher frequencies than those with longer time constants. Unfortunately, there is no simple way to calculate ideal frequencies for HFOV for an individual patient.

CO_2 transport during HFOV has been shown to directly relate to the oscillation frequency and tidal volume through a power law where the exponents of both frequency and tidal volume are positive (Figure 5). However, not all frequency-tidal volume combinations

are desirable, since some may lead to lung pressure swings or volume changes that are larger than those produced by conventional ventilation. The oscillatory frequency denotes the number of cycles per minute, measured in units of Hertz (Hz=1cpm). Intraalveolar pressure may depend on the oscillatory frequency. At frequencies close to the resonance frequency of the intubated respiratory system, higher alveolar pressure than tracheal pressure has been observed. The optimal oscillatory frequency is currently a controversial issue. In most studies of HFOV in infants, frequencies below 16Hz were used. In severe respiratory failure, if adequate $PtcCO_2$ cannot be obtained with maximal oscillatory volume (pressure amplitude), decreasing the oscillatory frequency to 10Hz will increase tidal volume and improve CO_2 elimination from the lungs. The use of a frequency greater than 15Hz results in an attenuation of the tidal volume, reducing CO_2 elimination.

During HFOV, transcutaneous monitoring of CO_2 ($PtcCO_2$) is beneficial in preventing inadvertent hyperventilation. When optimal lung volume is approached, compliance increases and tidal volume increases. Compliance improvement can be rapid, this should be followed an immediate decrease in oscillatory amplitude. Therefore, as MAP is increased to recruit optimal lung volume, oscillatory amplitude is adjusted to maintain $PtcCO_2$ or $PaCO_2$ between 40-45 mmHg until lung volume is optimized.

Factor Affecting Oscillatory Pressure

The extent to which the oscillatory pressure waveform is damped is influenced by the mechanical characteristics of the respiratory system. The impedance of the combined ventilator, circuit, endotracheal tube, and respiratory system is an important determinant of the efficiency of ventilation during HFOV. Impedance is a global term that encompasses the mechanical properties of Ela stance (1/compliance), resistance, and the inheritance. Although inheritance is essentially negligible at conventional ventilation frequencies, it assumes a much greater role at higher frequencies during HFOV. Impedance represents a mechanical barrier to flow and as it increases, higher-pressure swings are required to generate an equivalent flow. As pressure differences that drive flow also distend tissues, one of the major goals of HFOV strategies is to attain adequate gas transport with low tidal volumes while avoiding pressures that either over distend (causing barotrauma) or cause airway closure and alveolar collapse (atelectrauma). The distribution of impedance along the combined ventilated respiratory system impacts on the transmission of the amplitude of oscillatory pressure swings and flow to various lung compartments. Atelectasis alveoli will experience higher oscillatory pressures than normally aerated alveoli, whereas increased peripheral resistance increases the oscillatory pressures transmitted to proximal airways.

Inspiratory-expiratory ratio

The selection of inspiratory to expiratory time ratio (TI:TE) influences the delivery of pressure and volume to the lung. Traditionally, clinicians used asymmetric TI:TE ratios (inspiration shorter than expiration) to avoid the development of gas trapping during HFOV. Early studies [20-22] indicating mean pressures in the lung higher than those recorded at the trachea used low mean airway pressures that may have precipitated the development of choke points [23]. Using an optimal volume strategy, airways are splinted open [24], and providing the inspiratory and expiratory cycles are of equal duration and expiration is active rather than passive, there is negligible change in mean pressure between the airway opening and the lung [25]. In contrast, the use of a TI=33% of total cycle time actually results in a drop in the mean intrapulmonary pressure as a result of higher flow-dependent endotracheal tube resistance during inspiration compared with expiration resulting from higher flows during the shortened inspiratory phase. The magnitude of the pressure drop increases with increasing frequency, and decreasing endotracheal tube internal diameter and relative duration of the inspiratory component [26], and in part explains the need to increase MAP above that used with ventilation at more conventional rates when initiating HFOV with TI=33% of total cycle time. It has been proposed that the use of asymmetric TI:TE may exaggerate the normal asymmetry of inspiratory and expiratory velocity profiles as a result of the proportionately higher inspiratory flows, further enhancing the efficiency of gas mixing. However, studies [27,28] have failed to demonstrate a specific advantage of asymmetric flows on gas mixing efficiency. The consequences of TI:TE for gas mixing or the higher inspiratory flows associated with asymmetric TI:TE on induction of shear stress injury has not yet been adequately investigated. Additionally, as TI:TE ratio increased from 1:2 to 1:1, VT increased significantly. The effect of TI:TE is lost as frequency and pressure amplitude increased.

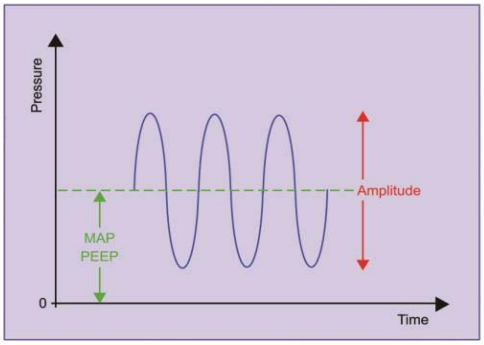

Figure 6: Ventilators differ in the shape of the pressure waveform delivered to the airway opening. Sinusoidal wave forms are normally delivered with equal inspiratory and expiratory cycle durations and thus has a single dominant frequency.
Note: The Mean Airway Pressure (MAP) is the PEEP (CPAP) around which the pressure oscillates. The peak-to-peak pressure or amplitude of oscillation (ΔP) is used, as an index of tidal volume but has no specific quantitative meaning, as it represents a composite of tidal volume and lung compliance.

Waveform

Ventilators differ in the shape of the pressure waveform delivered to the airway opening. Sinusoidal waveforms are normally delivered with equal inspiratory and expiratory cycle durations and thus have a single dominant frequency. When asymmetric TI:TE ratios are used, the fundamental frequency will be different during inspiratory and expiratory oscillatory cycles. Ventilators determine the TI:TE based on the relative durations of the respective components of the pressure waveform (Figure 6). For the square wave, this estimate is an approximation of inspiratory and expiratory flow cycles, which more accurately define the start of the inspiratory and expiratory periods. In contrast, a sinusoidal airway opening pressure waveform constructed with a 33% TI actually generates an inspiratory flow that

accounts for approximately 42% of the total cycle time. Therefore, the magnitude of the pressure drop across the endotracheal tube is less for a ventilator delivering sinusoidal pressure waveforms than for a square waveform ventilator [26]. Square waveforms are associated with sudden changes in flow and airway pressures, whereas more gradual and smooth changes are observed, using sinusoidal wave ventilation. The square wave ventilation at conventional breathing frequencies may be associated with increased incidence of air leak syndrome [29]. However, the impact of waveform shape and the rapidity of change in flow and pressure for shear stress and lung injury during HFOV has not been elucidated.

Frequency

Higher frequencies result in delivery of lower tidal volumes and also decrease the magnitude of the alveolar pressure swings [30]. In newborns, frequencies between 8 and 15 Hz are most often used [31]. Given the relative importance of VT in determining CO_2 clearance ($VCO_2 = f*VT^2$) [32], the goal of frequency selection needs to minimize the pressure swings to both proximal and distal lung compartments while not compromising the VT to the extent that insufficient ventilation takes place. From a mechanical point of view, this is likely to occur slightly below the resonant frequency of the lung [33].

Endotracheal tube

The endotracheal tube contributes over 50% of the total impedance of the respiratory system and accounts for approximately 90% of the inertance [34]. During HFOV, the resistance of the endotracheal tube is flow-dependent [35]. As resistance is inversely proportional to r4 (r=radius), small reductions in the internal diameter of the endotracheal tube (i.e., from secretions or change in endotracheal tube size) damps, the amplitude of the pressure waveform, and reduces resultant flow and VT. A decrease in endotracheal tube internal diameter also increases the magnitude of the drop in mean pressure amplitude between the trachea and the lung parenchyma for any given ventilator amplitude [36]. These effects are quite marked in narrow neonatal tubes [37].

Patient factors

Theoretical [37], *in vitro* [38], and *in vivo* [39] models of lung disease have demonstrated that damping at different points within the airways and alveoli is dependent on the distribution, homogeneity, and mechanical characteristics of disease within the respiratory system. In contrast, the traditional teaching approach for HFOV based on measurements made in models with highly compliant lungs, has emphasized extensive damping of the pressure waveform between the airway opening and the alveolar compartment [40].

HFOV was initially developed for use in the extremely noncompliant and immature lung of the premature neonate with RDS, characterized by relatively diffuse homogeneous atelectasis associated with surfactant deficiency. There is a sharp rise in the magnitude of the oscillatory pressure waveform transmitted to both alveolar and tracheal compartments at low compliance. The amplitude of the tracheal oscillatory pressure waveform increases with increasing peripheral resistance. Ventilation heterogeneity poses a problem at conventional ventilation frequencies because the distribution of gas is largely controlled by the distribution of regional lung compliance, and thus heterogeneous regional expansion and ventilation necessarily follow. As ventilation frequencies approach the resonance frequency, however, gas transport is less dependent on regional lung compliance [41] and increasingly governed by the resistive [20], inertive [40] and branching angle properties of the central airways [41]. Theoretical studies have indicated that compliant alveoli are effectively spared from excessive oscillatory pressures with the larger alveolar pressure swings being directed to the more poorly compliant compartments [37].

An increase in peripheral airway resistance, as might occur if ventilating with HFOV a patient with small airways disease, will result in a marked increase in the pressure swings in the airways proximal to the obstruction, despite the preservation of relatively small pressure and volume fluctuations delivered to the alveolar compartment. In such cases, setting ventilator frequency to the resonance frequency of the affected lungs will reduce the likelihood of excessive pressure excursions in the proximal airways and limit associated shear stress [33].

In summary, proximal oscillatory pressure (ΔP = amplitude of oscillation) transmitted to the distal alveoli depends on multiple variables, including endotracheal tube diameter, respiratory frequency, percentage of inspiratory time, airway resistance, lung compliance, and gravitational factors (e.g., lower *vs* upper lobe). Respiratory mechanics have a significant influence on the intrapulmonary oscillatory pressure during HFOV [44]. Low lung compliance can result in significant increases in distal oscillatory pressure transmission, approaching 20-30 % of proximal airway pressure amplitudes. Conversely, increases in peripheral airway resistance may decrease oscillatory pressure transmission to the distal alveolar compartment while increasing pressure excursions in the trachea and main stem bronchi. Also, changing the percentage of inspiratory time (e.g. from 33% to 50%) may influence oxygenation and ventilation by increasing the distal alveolar pressure and delivered tidal volume. These concepts suggest that development of optimal techniques for achieving oxygenation and CO_2 elimination (i.e., frequency, oscillatory pressure, percentage of inspiratory time, mean airway pressure) are critical for improving clinical outcomes with HFOV in neonatal RDS.

Ventilator Induced Lung Injury and HFOV

Lungs of patients with heterogeneously damaged, mechanical ventilation with normal or even low tidal volumes can lead to regional lung injury. Recruitment/DE recruitment denotes the situation whereby alveolar units open during inspiration and collapse again during expiration in atelectasis regions. This cycle of repeated opening and collapse results in high shear stress. This can further injure the lungs (atelectrauma), in particular at end-expiration. Reducing the magnitude of these cyclic fluctuations and application of higher Positive End-Expiratory Pressure (PEEP) levels can minimize ventilator-induced lung injury [45]. Over distension (volutrauma) develops when inspired air preferably distributes to the areas with higher compliance (nonatelectatic regions). Based on these concepts, various "lung-protective" strategies have been designed to minimize ventilator-induced lung injury. One strategy uses relatively small tidal volumes and PEEP titrated to a few centimeters of H_2O above the lower inflection point on the pressure-volume curve [46].

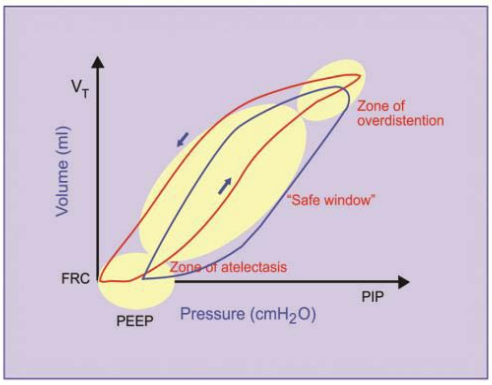

Figure 7: Volume curve of a diseased lung, two hazard zones exist; over distension and derecruitment and atelectasis. High end-expiratory pressures and small tidal volumes are needed to stay in the "safe" window. High-frequency oscillatory ventilation may have a larger margin of safety in keeping the lung open within the desired target range of alveolar over distension.

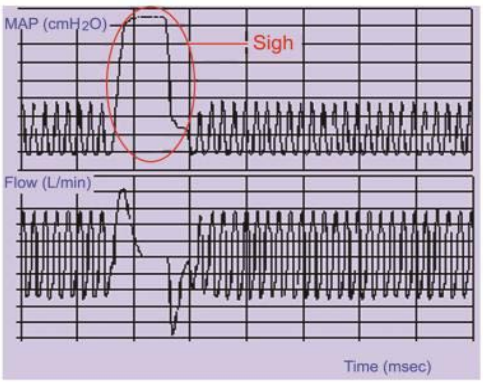

Figure 8: In animal studies when HFOV was combined with a sigh (sustained inflation, e.g. recruitment maneuver), there were larger mean lung volumes and improved oxygenation with HFOV.

Based on these concepts, various "lung-protective" strategies have been developed to minimize ventilator-induced lung injury. One strategy uses relatively small tidal volumes and PEEP titrated to a few centimeters of H_2O above the lower inflection point on the pressure-volume curve [47].

Within this context, HFOV can be viewed as providing alveolar ventilation with very small tidal volumes and thus, theoretically, could be viewed as providing the optimal lung-protective ventilator strategy. High frequency oscillatory ventilation has novel gas exchange mechanisms that contribute to better oxygenation and CO_2 removal. Because of these mechanisms, adequate gas exchange during HFOV is possible with extremely small tidal volumes, often less than the anatomic dead space (1-3 mL/kg). In addition, during HFOV, it is possible to maintain relatively high end-expiratory lung volume, without inducing over distension.

In the above pressure–volume curve of a diseased lung, two hazard zones exist; over distension and DE recruitment and atelectasis. High end-expiratory pressures and small tidal volumes are needed to stay in the "safe" window. High-frequency oscillatory ventilation may have a larger margin of safety in keeping the lung open within the desired target range of alveolar over distension [33] (Figure 7). Venegas & Fredberg developed a theoretical model to determine the optimal ventilator variables in patients with lung disease. Their model included models of gas exchange and lung mechanics, including the effects of lung inflation tidal volume and respiratory frequency in alveolar ventilation, nonlinear lung tissue compliance, and alveolar recruitment and DE recruitment. The model predicted that for RDS in neonates, the selected PEEP level was critical because detrimental consequences were increased at both high and low values of PEEP. Of interest, in the neonatal RDS patient, the choice of which respiratory frequency to use was not as critical for frequencies of >10 Hz. The analysis supported the use of HFOV in infant RDS and of ensuring adequate end-expiratory pressure. Additionally, their model predicted that the range of "safe" frequency-PEEP combinations would be relatively narrow and move to higher frequencies as lung compliance decreases. Also, if similar tidal volumes and levels of PEEP were applied at conventional frequencies (<50 breaths/min), CO_2 clearance would be compromised.

Animal studies

A number of animal studies that laid the groundwork for our current understanding of HFOV and ventilator-induced lung injury were published in the 1980s by the Toronto group led by Bryan [48] examined conventional mechanical ventilation and HFOV in models of oleic acid injury and lung lavage. They found that when HFOV was combined with a sustained inflation (e.g. recruitment maneuver), there were larger mean lung volumes and improved oxygenation with HFOV (Figure 8). They suggested that this approach of a lung volume recruitment maneuver and high mean airway pressures during HFOV could "more fully exploit the pressure volume hysteresis of unstable lung units than CMV." Hamilton, et al [49] examined oxygenation and lung pathology in rabbits with saline lavage–induced lung injury, ventilated with HFOV or conventional mechanical ventilation. HFOV provided marked improvements in oxygenation over 5hrs, and most importantly, the animals treated with HFOV had markedly attenuated lung injury as assessed by hyaline membranes. They concluded that "avoidance of low lung volume and large pressure-volume changes through the use of HFOV results in reduced pulmonary damage." This critical concept in the use of HFOV to mitigate ventilator-induced lung injury is still valid today.

McCulloch, et al [50] carried out a study aimed to assess whether the use of high MAP was important during HFOV. They ventilated rabbits after lung lavage using three different strategies: HFOV at high mean lung volume, HFOV at low mean lung volume, and CMV at a low mean lung volume. The latter two groups ventilated at low lung volumes had lower respiratory system compliance, more hyaline membranes, and more severe airway epithelial damage. These data demonstrated that maintenance of an adequately high mean lung volume is critical to minimize the lung injury caused by mechanical ventilation, and they also emphasized the importance of appropriate lung recruitment during HFOV.

Human trials

A number of human studies have been published in the last 2 decades. The results of these studies lack conclusive evidence supporting the preventive effect of HFOV on the development ventilator-induced lung injury. The first large multicenter randomized controlled trial, the HIFI trial [51], comparing HFOV with conventional mechanical ventilation showed that, babies

randomized to HFOV had a significantly greater incidence of major cerebral lesions and there was no difference in mortality or incidence of BPD. It was suggested that the failure to improve the incidence of BPD was due to the fact that, in this trial, HFOV was employed using a 'low-volume' strategy [52]. Ogawa, et al [53] reported the results of a multicenter randomized trial of HFOV as compared with conventional ventilation in preterm infants with respiratory failure. This randomized trial compared HFOV with conventional mechanical ventilation using the same entry criteria as the HIFI study (birthweight 750-2000 g). All patients received surfactant replacement therapy. The end points were survival and the incidence of BPD and of IVH. With either mode, the figures for the incidence of BPD were lower than in any other published study (9 and 13%), so low in fact that it would take very large numbers to show a statistical difference between the two modes of ventilation. There was no difference in the incidence of IVH, which was much lower than in the HIFI study.

Since the HIFI trial, eight further trials [54-60] have compared HFOV and conventional mechanical ventilation regarding effects on the incidence of CLD. Seven of these trials [54-60] employed HFOV using optimization of lung volume, but results were inconclusive. Six trials [54-60] reported the incidence of oxygen dependency at 36–37 weeks' post-menstrual age; four [54,56,57,60] showed that significantly fewer infants in the HFOV group required oxygen at this time, but two trials [57,58] failed to show any difference. Similarly, although not reported in all trials, the effect of HFOV on the incidence of BPD at 28-30 days and on death and BPD at 28-30 days was inconsistent. Besides the lack of conclusive evidence supporting the preventive effect of HFOV on the development of BPD, concern remains over the influence of HFOV on the incidence of major cerebral lesions. The initial HIFI trial [51] reported an increased incidence of both major Intraventricular Hemorrhage (IVH) and Periventricular Leukomalacia (PVL) in the HFOV group but most of the subsequent studies using a volume recruitment strategy have failed to repeat this finding. However, a trial of Moriette, et al. [58] again raised concern. These authors reported that babies randomized to HFOV had a significantly greater incidence of severe IVH (odds ratio 1.94; 95% confidence interval 1.05, 3.60). However, the difference was no longer significant when adjustment was made for the fact that more preterm infants in the conventional mechanical ventilation group were born to mothers with hypertension during pregnancy, a condition which is negatively associated with IVH.

A systematic review [61] looking at elective HFOV *versus* conventional mechanical ventilation for acute respiratory failure in preterm infants showed that, when considering only those trials employing HFOV using a volume recruitment strategy, this mode of ventilation was associated with significantly lower rates of BPD in survivors at 28-30 days (three trials, relative risk 0.53; 0.36, 0.76). Death or BPD at 28-30 days (three trials, relative risk 0.56; 0.40, 0.77), and oxygen use at 36-37 weeks' post-menstrual age or discharge (five trials, relative risk 0.72; 0.56, 0.93) were also significantly reduced. Reassuringly there was also no overall difference in the rates of IVH or PVL. However, the trials cited in this review span a period of 16 years, surfactant was not used in the early trials and the use of antenatal steroids was very variable. In addition, many of the early trials had only few extremely low birth weight (birth weight <1,000g) infants in whom the incidence of CLD is highest and some studies included infants up to 35 weeks' gestation. The time of starting HFOV also varied considerably between trials and often randomization did not occur until several hours after birth. Since it has been shown in rabbits that epithelial necrosis occurs very shortly after the onset of tidal breathing [62] waiting several hours before commencing HFOV may minimize the benefits of this mode of ventilation. Finally, only two trials reported any long term outcome [51,53]. The authors of this review concluded that "benefits of HFOV in terms of CLD appear to be outweighed by concerns about increased rates of pulmonary air leak and severe IVH. Until these issues are resolved HFOV cannot be recommended as the routine method of giving mechanical ventilation to preterm infants with respiratory distress syndrome" [61]. Since this systematic review, two large trials [63,59] published recently showed contrasting results. The results of the study by Johnson, et al [63] did not show a difference between the two modes of ventilation for the combined outcome of CLD or death. In contrast, Courtney, et al [59] found a small difference favoring HFOV. These two trials were very different in their ventilator strategy. The trial by Johnson et al provided target guidelines for blood gases and specified only the inspiratory time and ventilator rate. The rest of the ventilator management was at the discretion of the attending clinician, and reflects common NICU practice around the world. In the trial by Courtney et al., which compared HFOV with a sophisticated conventional ventilation strategy including both continuous tidal volume monitoring to avoid lung injury from volutrauma and protocolized weaning, infants on HFOV were intubated, on average, a full week earlier than infants on conventional ventilation, and had a lower incidence of CLD. The ventilator strategy in the study by Courtney et al. was strictly protocol based. Shah [64] extracted data from the Cochrane systematic review [65] for the trials comparing HFOV using high volume strategy *versus* conventional mechanical ventilation and combined that with the data from the trials by Johnson et al and Courtney et al. The resulting meta-analysis (seven trials and 2069 infants) showed a statistically significant reduction in the incidence of CLD or death in the HFOV group (summary RR 0.90, 95% CI 0.83 to 0.98; NNT 20, 95% CI 11 to 100). There was no evidence of difference in the incidence of grade 3 or 4 IVH (summary RR 0.97, 95% CI 0.78 to 1.19) or pulmonary air leaks (summary RR 1.04, 95% CI 0.87 to 1.25).

HFOV and intracranial pathology

One of the key controversies surrounding HFOV is related to concerns about a possible role of HFOV as a risk factor for the development of severe intracranial hemorrhage or periventricular leukomalacia. Potential mechanisms include pulmonary hyper expansion or high intrathoracic pressure leading to cerebral venous congestion, and hypocarbia resulting from the ease with which HFOV usually is able to ventilate the patient.

The conclusions of the published controlled clinical trials of HFOV in human infants regarding this question are summarized in the table below.

The HIFI trial suggested that HFOV is associated with an increased incidence of IVH or PVL. Variations in ventilation management and HFOV experience across study sites in the HIFI trial [51] may have contributed to the large intercenter differences in IVH, and have led some to question the validity of these results. By contrast, the early study of Clark, et al [54] and studies of Ogawa, et al. [53] Gerstmann,

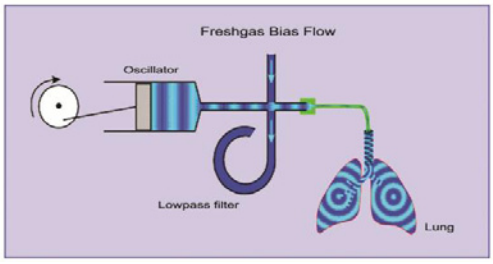

Figure 9: A classical high frequency oscillator is a device which consists of a piston pump with a variable frequency. The output of the pump is attached to the endotracheal tube by a four way connector. The stroke volume of the pump moving back and forth, which is delivered to the lungs is not equal to tidal volume entering the lung, since part of the oscillatory flow is lost via the length of the tubing, which acts as a low pass filter, or around the endotracheal tube. The fresh gas flow from an oxygen blender enters through one arm of the four way connector. The flow rate, controlled by a flow meter, determines mean airway pressure. The mean airway pressure can be adjusted independently by adjusting the flow of fresh gas. The three other ports are connected to noncompliant tubing which transmits the oscillation from the pump to the endotracheal tube and a low pass filter which allows excess fresh gas and CO_2 which diffuses from the lungs to exit. The low pass filter provides high impedance to high frequency events (oscillations) and low impedance to low frequency events such as continuous flow or spontaneous respirations.

et al. [55] Rettwitz-Volk, et al [60] Plavka, et al [56] and Thome et al [57] all found no increase in the incidence of IVH or PVL in the HFOV group. The trial by Gerstmann et al. found that for tidal ventilation the incidence of severe IVH was 11% compared with 4% for HFOV, whereas PVL incidence was 6% *versus* 8%. The latter is a trial of large premature infants (mean birth weight 1510 g). The two largest contemporary trials [63,59] published recently showed contrasting results. The results of the study by Johnson et al. showed a significant reduction in severe intraventricular hemorrhage and periventricular leukomalacia in the HFOV group. In contrast, Courtney et al. did not find a difference favoring HFOV. These two trials were very different in their ventilator strategy. The trial by Johnson et al. provided target guidelines for blood gases and specified only the inspiratory time and ventilator rate. The rest of the ventilator management was at the discretion of the attending clinician, and reflects common NICU practice around the world. On the other hand, the ventilator strategy in the study by Courtney et al. was strictly protocol based.

The results of these latter trials are somewhat contradicted by results of the study of Moriette, et al [51,66]. Despite using an optimum volume strategy of HFOV there was a significant increase in severe IVH (14% for conventional ventilation *versus* 24% for HFOV, OR 1.94, CI 1.05 to 3.60, $p<0.05$). The difference was no longer significant when presence of maternal hypertension was factored in. The mean $PaCO_2$ in the conventional ventilation group was significantly higher than that of the HFOV group 6 hours after randomization (39 *versus* 35 mm Hg, $P<0.001$). The relevance of this latter finding is unclear, however, because there was no difference in the incidence of PVL.

Neonatal Oscillators

High frequency oscillatory ventilation is delivered by specialized, widely variable apparatuses (piston pump, ball valve interrupter or acoustic speaker) generating respiratory rates of 300-2400 cycles per minute (Figure 9). Regardless of the exact form of high frequency oscillation, the intent is to provide adequate oxygenation and ventilation while maintaining FIO_2 and MAP and/or PIP as low as is practical in the hope of minimizing pulmonary damage.

A classical high frequency oscillator is a device, which consists of a piston pump with a variable frequency. The output of the pump is attached to the endotracheal tube by a four-way connector. The stroke volume of the pump moving back and forth, which is delivered to the lungs is not equal to tidal volume entering the lung, since part of the oscillatory flow is lost *via* the length of the tubing, which acts as a low pass filter, or around the endotracheal tube. Thus, the volume of gas entering the lungs is related to the ratio of the patient's impedance to the tubing impedance at any particular frequency. The fresh gas flow from an oxygen blender enters through one arm of the four-way connector. The flow rate, controlled by a flow meter, determines mean airway pressure. The mean airway pressure can be adjusted independently by adjusting the flow of fresh gas. The three other ports are connected to noncompliant tubing, which transmits the oscillation from the pump to the endotracheal tube and a low pass filter. The low-pass filter allows excess fresh gas and CO_2 which diffuses from the lungs to exit. The low pass filter provides high impedance to high frequency events (oscillations) and low impedance to low frequency events such as continuous flow or spontaneous respirations. The pressures close to the endotracheal tube is continuously monitored with a pressure transducer. The peak-to-peak pressure or amplitude of oscillation (ΔP) is used as an index of tidal volume but has no specific quantitative meaning, as it represents a composite of tidal volume and lung compliance.

Principles of Operation

There are three distinguishing characteristics of HFOV: the frequencies range from 5 to 40 Hz (300 to 1,800 cycles per minute), active inspiration and active expiration, and tidal volume about the size of the dead space.

The management of a patient with HFOV is based on a few simple principles:

Oxygenation is decoupled from ventilation in that changes made to alter oxygenation have little effect on CO_2 elimination from the lungs, and conversely, changes made to effect $PaCO_2$ change have little effect on oxygenation.

To change oxygenation, lung volume has to be adjusted, as there is a close relationship between lung volume and surface area for gas exchange. Because during HFOV, lung volume is established with MAP, the MAP adjustment will have a profound effect on oxygenation. After optimizing lung volume with an FIO_2 less than 0.30 the MAP may be slowly reduced. Because of the hysteresis of the pressure volume relationship of the lung on the deflation limb, the reduction in MAP will not result in a significant loss of lung volume. However, when MAP drops below the critical closing pressure oxygenation may suddenly fall. Because the lung volume has shifted back to the inflation limb it may require a re-recruitment of lung volume. Re-recruiting the lung volume is done by increasing MAP up the inflation limb to an optimum lung volume and then slowly decreasing MAP and lung volume on the deflation limb.

Manipulating the oscillatory tidal volume attains control over CO_2 clearance from the lungs. In HFOV, $PaCO_2$ is closely related

Table 1: The conclusions of the published controlled clinical trials of HFOV in human infants regarding this question are summarized in the table below.

Author /Year	Sample size	Outcome
HIFI. 1989 [49]	673	Significant increase in both severe intraventricular hemorrhage and periventricular leukomalacia
Clark, et al. 1992 [52]	83	No difference in intraventricular hemorrhage*
HiFO. 1993 [50]	176	Significant increase in severe intraventricular hemorrhage in the HFOV group*
Ogawa, et al, 1993 [51]	92	No difference in intraventricular hemorrhage*
Gerstmann, et al. 1996 [53]	125	No difference in intraventricular hemorrhage or periventricular leukomalacia
Plavka, et al. 1997 [54]	43	No difference in intraventricular hemorrhage or periventricular leukomalacia
Rettwitz-Volk, et al. 1998 [58]	96	No difference in intraventricular hemorrhage or periventricular leukomalacia
Moriette, et al. 2001 [56]	273	Significant increase in severe intraventricular hemorrhage
Johnson, et al. 2002 [61]	797	Significant reduction in severe intraventricular hemorrhage and periventricular leukomalacia in the HFOV group
Courtney, et al. 2002 [57]	481	No difference in severe intraventricular hemorrhage or periventricular leukomalacia

*No data on periventricular leukomalacia.

to the delivered oscillatory volume (expressed as peak-to-peak pressure=amplitude of oscillation=delta pressure). The adjustment of oscillatory tidal volume (amplitude of oscillation) is based on the observed chest shaking, transcutaneous CO_2 monitoring and arterial blood gases. When lung volume is optimized, compliance improves and tidal volume is increased. This compliance improvement requires an immediate decrease in oscillatory amplitude to avoid hypercapnia.

Oscillatory frequency is kept unchanged at 15Hz (900cycles/minute) throughout the ventilator treatment. The frequency of 15Hz is used for reasons of convenience and practicality, since it allows shaking to be used as a clinically detectable index of transmission of oscillations to the lungs. This visual feedback is lost at higher frequencies as no chest movement is appreciated at frequencies greater than 25Hz. It is important to note that the management of HFOV is very different from conventional mechanical ventilation. Thus the complex and unpredictable interaction between rates, peak and end expiratory pressure which govern O_2 and CO_2 exchange, during conventional mechanical ventilation are not observed thus allowing for easy and separate adjustment of CO_2 elimination and oxygenation.

Immediately after intubation, MAP is set at 10cm H_2O and increased stepwise by 1-2 cm H_2O until the FIO_2 decreases below 0.30 (optimum lung volume strategy). Thereafter, MAP is decreased in a stepwise fashion by 1-2 cm H_2O, as long as oxygenation does not deteriorate.

In infants switched from conventional mechanical ventilation to HFOV, lung volume, while on conventional mechanical ventilation at the time of transfer to HFOV, MAP is set 1-2 cm H_2O higher than that being used on conventional mechanical ventilation and increased stepwise by 1-2 cm H_2O to increase lung volume along the pressure volume curve. Transcutaneous CO_2 and oxygen saturation monitoring, arterial blood gases, blood pressure monitoring and chest x-ray should follow the incremental changes. As incremental MAP increases are carried out, FIO_2 is decreased to keep PaO_2 around 60 mm Hg and oxygen saturation in the range of 91-94 %. In the fully recruited lungs, the FIO_2 is reduced to less than 0.30. Optimal lung volume on chest x-ray correlates with obtaining an 8-9 posterior rib expansion on the right hemi diaphragm and decreased lung opacification.

During the process of weaning from HFOV, it is important to avoid causing atelectasis by dropping the MAP below the critical closing pressure of the lungs. The FIO_2 should be weaned first in response to good oxygenation and the MAP should not be weaned until the FIO_2 is less than 0.3. Very low-birth weight infants can usually be intubated as soon as they have been weaned to MAP of 5 to 7 cm H_2O. Larger infants can be intubated from higher settings.

Indications for HFOV

The use of small tidal volumes at high frequencies allows more uniform lung inflation and causes less damage to severely noncompliant lungs than do the larger tidal volumes of conventional ventilation. Most patients with uniform lung disease who require high inspiratory pressures (≥25cm H_2O) could benefit from HFOV.

HFOV may be efficacious for patients with severe uniform non-RDS lung disease, such as pneumonia or persistent pulmonary hypertension.

HFOV may also be useful in patients with severe no uniform disease, such as aspiration syndromes. When HFOV is used in infants with aspiration syndromes, slower frequencies should be used because of the longer time constants, to minimize the chance of air-trapping.

HFOV may have a role in patients with pulmonary hypoplasia, such as is seen with diaphragmatic hernia. High-frequency oscillation allows maintaining adequate gas exchange while using extremely small tidal volumes.

HFOV could be a preferable mode of ventilation when severe chest wall restriction or upward pressure on the diaphragm from abdominal distention interferes with tidal ventilation. Increased intra-abdominal pressure results in upward pressure on the diaphragm, reduces diaphragmatic excursion, and results in decreased compliance of the respiratory system in newborns with acute intra-abdominal disease, such as necrotizing enter colitis, or postoperatively in infants with gastroschisis, omphalocele, or diaphragmatic hernia. Large tidal volume ventilation further exacerbates the hemodynamic compromise normally caused by positive pressure ventilation.

HFOV may be useful for the treatment of air leak syndromes: pulmonary interstitial emphysema and Broncho pleural or tracheoesophageal fistula.

A trial of HFOV is appropriate in term infants with severe respiratory failure who are potential candidates for ECMO.

In infants with significant parenchymal lung disease, HFOV in combination with inhaled nitric oxide is more effective than inhaled nitric oxide delivered with conventional ventilation.

Potential Complications of HFOV

There are potential complications that may be encountered while managing an infant with HFOV.

Mucus plugging

Airway impaction with mucus has been report in infants after prolonged use of HFOV, which could relate to inadequate humidification. On HFOV, it is essential to adequately humidify the breathing gas. Inadequate humidification may cause irreversible damage to the airways, obstruction of the airways with viscous secretions and deteriorate pulmonary situation. On the other hand, excessive humidification can lead to condensation in the ventilator circuit, the endotracheal tube and the airways, and failure of HFOV. The small tidal volumes of HFOV may not breathe through mucus plugging and condensation in the airways effectively. When mucus plugging of the endotracheal tube and the airways are not responsive to frequent suctioning the infant may be switched to conventional mechanical ventilation. During HFOV frequent suctioning is not required in the first 24-72 hours; however as compliance improves suctioning may be required every 6-8 hours.

Cardiovascular compromise

The use of relatively high MAP (CPAP) during HFOV raises a concern that the high lung volumes may have adverse effect on venous return and cardiac output. However, the comparison of cardiac output during HFOV and conventional mechanical ventilation has failed to show differences between the two modalities of ventilation. Lung over distension may cause cardiovascular compromise. Infants treated with HFOV may be less tolerant of myocardial dysfunction or hypovolemia than infants on conventional mechanical ventilation. Myocardial dysfunction or hypovolemia may cause ventilation-perfusion mismatch which will counter the positive oxygenation effects of optimal lung volume recruitment. The treatment of infants with myocardial dysfunction or hypovolemia consists of inotropic drugs and intravenous fluid administration. Monitoring of heart rate and blood pressure, echocardiographic assessment for blood volume status and serial chest x-rays for the evaluation of lung volume are helpful in the management of infants ventilated by HFOV.

Loss of lung volume

While on HFOV, suctioning requires disconnecting the endotracheal tube. This may result in a significant fall of lung volume, especially in surfactant deficient infants. On reinstitution of HFOV, MAP may need to be increased above the previous MAP to attain re-recruitment of lung volume. This is usually accomplished at a MAP 1-2 cm H_2O higher than the previous MAP and weaning to the previous MAP as oxygenation improves. Similarly, to instill exogenous surfactant into the endotracheal tube while on HFOV requires interrupting the circuit with loss of lung volume. Re-recruitment of lung volume after instillation of surfactant can be accomplished by raising MAP by 1-2 cm H_2O above the previous MAP and weaning back to baseline MAP as oxygenation improves. Since HFOV results in a better recruitment of lung volume and a rapid reduction in oxygen requirement (FIO_2 less than 0.30), subsequent doses of exogenous surfactant are less needed for infants on HFOV.

Conclusion

HFOV is a ventilator technique that can provide adequate gas exchange using very small tidal volumes. This allows ventilating patients at relatively high mean lung volumes, minimizing the risks of volutrauma and of atelectrauma. Animal data are quite convincing that HFOV is an ideal lung-protective ventilator strategy, but there is a paucity of clinical data supporting this contention in humans. As with any new technology, there is an ongoing process of determining optimum ventilation approaches for clinical management of infants with respiratory failure. The combination of early use of HFOV with optimal lung volume recruitment and surfactant administration, offers the best treatment combination in the infant with RDS.

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