Review Article

A review of high-frequency oscillation

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High frequency ventilation has been defined as ventilation at higher than normal frequencies with smaller than normal tidal volumes.[1] Within this definition are included high frequency positive pressure ventilation (HFPPV), high frequency jet ventilation (HFJV) and high frequency oscillatory ventilation (HFO). These three modes differ not only in the frequencies used (HFPPV, 1–2 Hz; HFJV, 1–3 Hz; HFO, 3–30 Hz); but also in the ventilators and circuits required, their physiologic impact, and potential clinical uses. Because of this diversity within the HFV group, conclusions drawn from studies on any one of the above modes may not apply to others in the group. This review will be concerned only with HFO, which will be arbitrarily defined as ventilation within the frequency range 3–30 Hz (180–1800 breaths per minute) and at tidal volumes less than, or approximating dead space. Most studies of HFO have been done in the range 10–20 Hz. Within the frequency range defined for HFO considerable heterogeneity of gas transport mechanisms and physiologic impact of pressure profile may exist. The best frequency at which to oscillate, the criteria which determine best frequency, and the clinical importance of this form of ventilation are yet undetermined.

Key words

VENTILATION: high frequency oscillation, high frequency ventilation, mechanical ventilation.

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Gas transport mechanisms

As yet no consensus exists as to exactly how gas is transported during HFO, although a number of possible mechanisms have been proposed. As the tidal volume of ventilation approaches and then falls below anatomic deadspace the traditional Bohr model fails to predict the transport of the respiratory gases. Fredberg[2] published the first analysis of transport during HFO. His model proposes that transport at small tidal volumes occurs secondary to turbulent mixing induced in the bronchial tree by the oscillations. Since that paper a substantial amount of literature has accumulated on the topic. Two excellent reviews have recently been published; the review by Chang[4] is the shorter of the two, while Kamm's[3] is more technical and includes a review of the literature.

Gas transport during conventional mechanical ventilation (CMV) may be described by the Bohr model. In this analysis the lung is divided into two compartments – one represents the aggregate deadspace (V_D), the other the total alveolar volume. With each breath the tidal volume (V_T) flows through the deadspace compartment to the alveolar compartment, where it is assumed to mix perfectly with the resident gas. The net transport of alveolar gas over a cycle is proportional to ($V_T - V_D$). However as V_T decreases this model fails in predicting the magnitude of gas flux. During HFO, when tidal volumes are often less than deadspace, alternate models are required since ($V_T - V_D$) is negative and no transport of gas would be predicted. Three of the major mechanisms that have been proposed to account for transport during HFO will be discussed – direct alveolar ventilation, dispersion and pendelluft.

Direct alveolar ventilation

It has been demonstrated from plastic casts of the bronchial tree that the path length from airway opening to alveolus (and thus regional deadspace) varies for different parts of the lung.[5] The distribution of path lengths approximates a normal distribution. In the Bohr analysis of gas transport the fact that regional deadspace varies is ignored – this is a reasonable simplification with large tidal volume ventilation but in part accounts for the failure of the Bohr model as tidal volumes approach deadspace. Because of the variability in path lengths some alveoli (those with short path lengths) are directly ventilated even at tidal volumes below deadspace. The number of alveoli directly ventilated will depend on the tidal volume and the distribution function characterizing the path lengths. An estimate of the contribution of direct alveolar ventilation to gas transport during HFO has been made by Kamm.[3] He predicts that for tidal volumes greater than 0.8 V_D this mechanism may account for a significant fraction of gas exchange. As tidal volume falls there will be fewer alveoli directly ventilated and at volumes below 0.5 V_D the contribution of direct ventilation to total flux is negligible.

Dispersion

For those alveoli not directly ventilated, other mechanisms which can induce gas transport have been proposed. These are based on the concept that the high frequency oscillations induce gas mixing within the deadspace. Figure 1 illustrates how mixing and smaller than deadspace tidal flows can result in gas transport. The deadspace and a subtending alveolar region are schematically illustrated; the deadspace has been divided into subcompartments of volume V_T (the tidal volume of oscillation). We start the cycle in end inspiration (a) and assume as initial conditions that the CO_2 concentration is zero in the deadspace and C_A in the alveolus. During the expiratory phase (b), gas of volume V_T and concentration C_A will move into the deadspace compartment. If no mixing occurs between this plug of gas and the resident deadspace gas, during the next inspiration this plug would be returned to the alveolus. The net transport of CO_2 occurring over the cycle will have been zero, as predicted by the Bohr model.

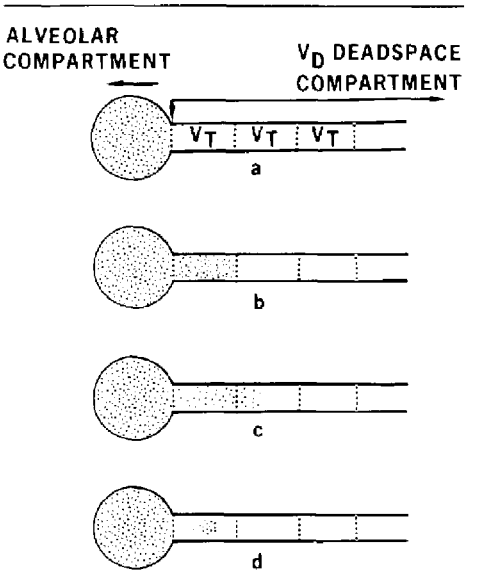

FIGURE 1 Schematic illustrating the interaction of smaller than deadspace tidal volume oscillations and mixing to produce gas transport: (a) end inspiration, (b) end expiration, (c) mixing, (d) end inspiration.

Now consider the cycle during HFO, where mixing is assumed to occur within the deadspace compartment. A bolus of gas of volume V_T and concentration C_A again enters the deadspace (b),

but this time mixing of this bolus with the resident deadspace gas occurs (c). During the subsequent inspiration a volume of gas VT is returned to the alveolus, but, by virtue of the mixing process its composition has changed, i.e., the CO_2 concentration is less than CA. Thus net transport of CO_2 into the deadspace has occurred over the cycle. The amount of CO_2 left behind in the deadspace will depend on the extent of the mixing. In subsequent cycles the process will be repeated, CO_2 will be transferred between successive compartments and will eventually reach the airway opening. In contrast to conventional ventilation where a given molecule of CO_2 traverses the deadspace in a single breath, several cycles are required during HFO. The mixing has been isolated as a separate step in (c) for illustrative purposes but in fact occurs over the ventilatory cycle. Mitzner *et al.* have developed a mathematical model of the process based on the above concepts.[7]

The mixing mechanisms operative in a particular portion of the bronchial tree depend on the flow patterns induced there by the pressure oscillations at the airway opening.[6] They include convective streaming (due to asymmetry of inspiratory and expiratory profiles induced by bifurcations[8,11]) and Taylor turbulent and laminar dispersion (axial convection coupled with radial diffusion[6]). The transport which results may be described in time and space by equations analogous to Fick's law for diffusion but with the diffusion coefficient replaced by a dispersion or diffusivity coefficient; this has led to the description of the process as "enhanced diffusion." The dispersion coefficient represents the intensity of the mixing process and is a function of the frequency and tidal volume of ventilation.

Pendelluft

Pendelluft refers to the exchange of gas between parallel lung units because of time constant inhomogeneity. This will make the gas contained in the airways common to the parallel units undergoing interchange uniform in composition. The volume of the effective respiratory zone will thus be increased (i.e., extended into the airways) and the tidal volume required for direct alveolar ventilation will be reduced.[3,14]

Experimental studies

There have been a number of studies which have related gas flux to frequency and tidal volume during HFO. Because of the different transport mechanisms involved during HFO the relationships between these variables are not as simple as during CMV.

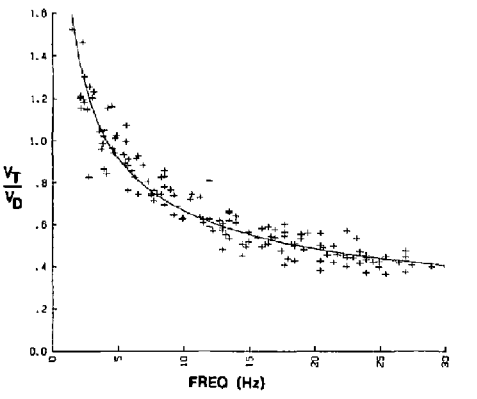

FIGURE 2 Tidal volumes (expressed as a fraction of deadspace) required at various frequencies for isocapnoia.

In dogs we determined, by plethysmography, the tidal volumes required for isocapnoia at a number of frequencies in the range 3–30 Hz. We found:

(1) Gas flux (CO_2 transport) is proportional to $fV_T^{2.2}$. Similar relationships have been found from a modified N_2 washout technique in dogs[1,7] and in hardware models of the bronchial tree.[12,13] The $fV_T^{2.2}$ relationship is consistent with the qualitative and quantitative[15] observations made by several groups that increases in frequency are less effective in increasing gas flux than are proportionate increases in tidal volume.

(2) The minute volumes ($V_T \times f$) required for isocapnia at 15 Hz are of order of ten times those required during CMV, reflecting the fundamentally different transport mechanisms involved in the two forms of ventilation and the relative "inefficiency" of dispersion compared to direct alveolar ventilation.

(3) Figure 2 relates tidal volume of ventilation (as a fraction of deadspace) required for isocapnia to frequency over the range 3–30 Hz. The exponential nature of this curve demonstrates that little is to be gained by oscillating at frequencies above 15 Hz in the dog if the aim is to minimize tidal volumes. The decrease in the absolute slope of the curve as frequency increases most likely reflects the decreasing contribution of direct alveolar ventilation to gas

transport and the greater reliance on dispersion as tidal volumes get smaller.

The effect of changes in airway resistance on gas exchange during HFO has been investigated in both humans and dogs. Rossing *et al.*[20] studied the effect of histamine induced bronchospasm on gas exchange in dogs. When compared to control values a decrease in transport efficiency (CO_2 output for a given minute volume of ventilation) was observed and this was most marked at the higher frequencies. They attributed the decrease in transport efficiency to the histamine-induced impedance mismatch between proximal and distal airways. Because of the increased peripheral resistance and high airway pressure, the tidal volumes distended the proximal upper airways (which acted as a shunt capacitance) causing a frequency-dependent decrease in the fraction of tidal volume entering the more distal airways. They demonstrated concomitant distension of proximal airways on cineradiography, supporting their hypothesis.[21] The same group found that in humans isoproterenol increased gas transport efficiency.[19]

Clinical data is limited.[10,18,19] Rossing *et al.*[18] found that in a group of chronically ventilated patients CO_2 elimination at fixed tidal volumes plateaued at frequencies above 3 Hz. They suggested the curve may have plateaued because their patients had peripheral airways disease and that the tidal volumes were lost in expanding the large airways (cf. the dogs in whom histamine was infused).

Obviously more studies are required on the influence of lung mechanics on gas transport during HFO. Further data on gas exchange in humans are needed to guide in selection of the most appropriate frequencies to use during this form of ventilation.

Ventilators and circuits

Ventilators and circuits employed during HFO have been diverse.[16,22] The system must be able to: (i) generate oscillatory pressure patterns at the airway opening to induce mixing, (ii) maintain the concentration gradients required for gas transport by delivering oxygen to and removing CO_2 from the upper end of the airway, and (iii) monitor parameters of ventilation and detect system malfunction.

Ventilators

Piston pumps have been used by most groups to provide the oscillations although flow interrupters employing ball valve mechanisms (the Emerson device) or rotating valves,[16] and biphasic jets[23] have also been employed. Tidal volumes are relatively small during HFO but because of the large pressure drops associated with high velocity oscillatory flows high circuit pressures (e.g., 100 cm H_2O) may need to be generated. The combination of small tidal volumes and high operating pressures makes economy of compressible volume in both circuit and ventilator a factor in design – increases in compressible volume would require larger tidal volumes from the ventilator to generate a given pressure amplitude at the airway. The most common respiratory waveform used during HFO reflects the piston used to generate it, i.e., a complete sinusoid with a negative expiratory phase and 1:1 IE ratio. Little work exploring the optimal pressure pattern for this form of ventilation (i.e., the I:E ratio, importance of a negative phase) has been done. Ideally the pressure pattern delivered from the ventilator should be variable. The ventilator should as well be easily cleaned, quiet during operation and be able to withstand the mechanical stresses attendant with delivering over a million oscillations per day.

Circuits

The high frequencies and low tidal volumes guide circuit design. The low tidal volumes require that compressible volume be minimal. The high frequencies preclude the use of an expiratory valve to ensure constant volume ventilation (as used during CMV) because the response times of mechanical valves are inadequate. Two major circuit designs have evolved to date. The first is the T piece circuit illustrated in Figure 3.[24] Both oscillations and the fresh gas flow (FGF) (also called bias flow) are introduced into one limb of the circuit; the other limb of the T (the low pass filter) provides the exit for the FGF and a fraction of the oscillatory volume. The low pass filter (LPF) consists of a long piece of tubing – ideally it provides a low resistance to the steady FGF but a high impedance to the oscillations. The fraction of piston stroke volume delivered to the patient is a function of the relative impedance of the patient and low pass filter to oscillatory flow; thus the tidal volume entering the patient's lungs is indeterminate with this system and may vary with changes in patient impedance. The mean airway pressure generated in the circuit

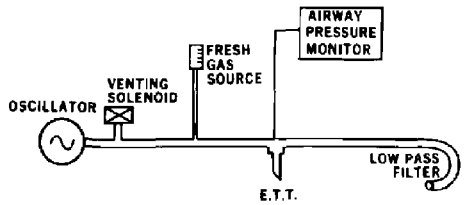

FIGURE 3 T-piece circuit. The FGF and a fraction of the oscillations exit the LPF. The solenoid vents the circuit to atmosphere should mean pressure exceed a preset limit.

(which determines lung volume) is a function of the fresh gas flow and resistance of the LPF. The advantages of this circuit are its simplicity and the fact that it allows spontaneous respirations by the patient through the low resistance LPF pathway. The second circuit design produces a functionally closed system for the oscillations. The circuit has no LPF; it introduces the FGF to the top of the ETT by a high impedance source sink arrangement – the FGF is supplied to the circuit through one restricting orifice and evacuated by suction through a second.[5] These orifices provide a very high impedence to oscillatory flow and thus the circuit has the advantage that, except for compressed volume and circuit leaks, the set piston volume is the volume delivered to the patient. The disadvantages of the circuit are, first, it is complex because it depends on a balanced inflow–outflow to prevent explosion or implosion; and second, it does not allow spontaneous respirations by the patient.

The fresh gas flow maintains the gradients not only for the respiratory gases but also for water vapour and heat exchange. High flow rates maximize gradients for gas exchange but create problems with humidification, heat loss, and potential for rapid pulmonary hyperinflation and barotrauma, should the exit for the FGF become obstructed. FGF's of 5–10 litres per minute (lpm) have been adequate in our paediatric patients and dog studies, and Soloway *et al.*[25] have not demonstrated a significant effect on gas exchange of decreasing the FGF from 27 to 12 lpm in their circuit (the "closed" system discussed above). Thus the fresh gas flows employed during HFO with piston systems can be much lower than minute ventilation and thus much easier to manage from the standpoints of humidification, safety and economy of gases than jet ventilators or flow interrupters where FGF is equivalent to minute ventilation.

Monitoring

Continuous monitoring of the driving function (tidal volume and frequency) and response (airway pressures and gas exchange) during HFO would be ideal but, unfortunately, limited by current technologies. A robust and practical instrument for measuring flow during HFO is not presently available – conventional screen and capillary tube pneumotachs were not designed for the high velocity oscillating flow patterns generated during HFO, exhibiting both high impedance and alinearity at these frequencies.

Measurements of both mean and dynamic airway pressures are useful during HFO. The mean airway pressure (MAP), reflects the lung volume which is oscillated and, like PEEP during CMV, may be manipulated to affect oxygenation. Monitoring of MAP is incorporated into a "safety package" that controls a solenoid which allows the circuit to vent to atmosphere should high circuit pressures be inadvertently generated (e.g., as a result of obstructure of the LPF).

Dynamic pressure measurements during HFO are of interest because they reflect the interaction of the lung and the forcing waveform. Unfortunately this measurement is complicated by two factors. The first is the requirement for adequate dynamic response of the pressure monitoring system which must be proven rather than assumed.[58] The second is that, unlike CMV, dynamic pressure swings are up to ten times higher within the circuit than in the trachea. This is a consequence of the high impedance to oscillatory flows of the endotracheal tube, and the high flow rates generated through it. The tracheal pressure is a much better reflection of both the stresses applied to the lung and of changes in lung mechanics than is circuit pressure. Unfortunately this is a difficult pressure to continuously monitor because of the tendency for a tracheal catheter to partially or completely obstruct. This problem, along with that of frequency response, may be solved with the use of a micromanometer tip (Millar) catheter, but only at considerable expense.

Dynamic mechanical responses

The dynamic response of the pulmonary parenchyma to HFO is central to many of the questions raised regarding the clinical usefulness of this form

of ventilation. It determines not only the potential for barotrauma, but also affects inter- and intra-regional gas distribution, fluid balance and metabolic function.

In 1956 Otis[26] published an analysis of the consequences of unequal time constants (RC) throughout the lung. His model predicts that as frequency increases, (i) the distribution (spatial) of ventilation becomes more dependent on regional resistance rather than compliance, and (ii) phase differences (temporal) in inflation of various parts of the lung occur giving rise to pendelluft (gas exchange between units in parallel). One would expect the impact of differences in time constants on the mechanical response of the lung to be even greater at the higher frequencies employed during HFO.

Lehr[27] has demonstrated that the excised lung does not respond isotropically to low tidal volume oscillations applied at the trachea. Marked non-uniformities in both extent and phase of expansion of various regions of the lung develop both between lobes and between regions of individual lobes. In a more detailed study[28] he subjected excised dog lungs, which had been marked with dots to form 80 squares, to 1, 15 and 30 Hz oscillations with 50–100 ml tidal volumes and photographed them with a strobe light. At 1 Hz the lung behaved isotropically – the sides of squares painted on the lung expanding uniformly and in phase. In contrast at 15 and 30 Hz the sides or diagnols of the squares were often out of phase – with differences of up to 180° between perpendicular elements. Within the constraints of the intact thorax one might expect the degree of such secondary motions to be less, but they undoubtedly exist to some extent. The implications of this dynamic pattern of expansion are two-fold. First, during HFO parenchymal stresses and strains may be more marked than predicted from consideration only of the tidal volumes employed and the static pressure volume curve of the lung. Both mean and dynamic alveolar pressures could be greater than the corresponding tracheal pressures. Second, phase differences in expansion between regions imply that pendelluft may be marked. Lehr has described "circulating currents" – these would tend to homogenize gas composition between regions. Examination of lungs by EM after 3–8 hours of HFO has not revealed any damage secondary to these asynchronous patterns of expansion.[29]

Because of the high minute volumes of ventilation used during HFO the potential for dynamic hyper-inflation is of concern.[30,16,60] The equation related the factors determining the end-expiratory lung volume above FRC (Vo) for conventional ventilation was formulated by Vinegar:[31]

$$Vo = \frac{V_T}{\exp\left(\frac{60\,K\alpha}{f}\right) - 1}$$

where V_T and f are the tidal volume and frequency of ventilation, K is the slope of the expiratory flow volume curve (inversely proportional to the RC time constant), and α is the time fraction spent in expiration. Thus, the degree of hyperinflation occurring during HFO will depend on the balance of ventilatory (f, V_T) and patient (resistance and compliance) parameters. The importance of an active expiratory phase (i.e., reverse piston stroke on the ventilator) in preventing hyperinflation is not known *in vivo*, although it appears useful *in vitro*.[23]

Saari *et al.*[60] have examined lung volumes during HFO in a series of eight patients. They found that, (i) in any one patient the degree of hyperinflation correlated with flow amplitude ($f \times V_T$), (ii) their patient with the lowest respiratory system compliance exhibited negligible trapping, and (iii) the degree of hyperinflation was not reflected by their measurement of mean airway pressure. In studies of rabbits with acute lung injury we found that the volume change induced by applying HFO at a given mean airway pressure was the same as that induced by a static pressure of the same magnitude.[32] Thus, if gas trapping occurred during HFO it was reflected by our measurement of MAP at the top of the circuit. In summary, the potential exists for global or regional gas trapping in this as in other forms of ventilation if V_T is large, or if K decreases because of either high respiratory system compliance or increased resistance to expiration; the latter may occur with inappropriate circuit design or with flow limitation secondary to airways disease. Until it is determined which subsets of lung disease are prone to hyperinflation, it is important to monitor for this complication with either (i) inductance plethysmography, (ii) estimates of alveolar pressures as reflected by respiratory system relaxation pressure measured after airway occlusion,[30] or, (iii) estimates of pleural pressure by oesophageal pressure,[63] and to recognize it as a possible cause for cardiovascular decompensation.

Effects on distribution of ventilation and perfusion

The distribution of pulmonary blood flow in dogs has been studied during HFO by two different techniques. McEvoy *et al.*[33] compared both the vertical and centripetal distribution of microspheres injected into dogs during CMV and HFO. Schmid[34] studied the distribution of ^{133}Xe injected into the right atrium of dogs with scintillation counters on the chest wall. Both groups found no difference in the distribution of perfusion during HFO compared to CMV – i.e., perfusion remained gravity dependent.

Distribution of Ventilation

Ventilation, on the other hand, might be expected to show changes in distribution during HFO because the pressure pattern applied to the lung is so different from that of conventional ventilation.

The distribution of ventilation during HFO differs from that during CMV in several ways: (i) it is more uniform; (ii) it is less dependent on regional compliance; and (iii) it is influenced by inter- and intra-regional mixing. Brusasco *et al.*[35] have studied the regional distribution of ventilation in the supine dog using ^{133}Xe and scintillation counters. During HFO at 15 and 30 Hz with tidal volumes less than two-thirds of deadspace longitudinal (airway to alveolus) ventilation was uniformly distributed to dependent and non-dependent areas. In contrast ventilation at 5 Hz with volumes greater than two thirds deadspace resulted in greater ventilation of dependent areas. (CMV as well results in greater ventilation of dependent areas.) The uniform distribution of ventilation during HFO may be due to an altered distribution of regional impedances and the different transfer functions relating minute volumes of ventilation (regional V_{TIDAL} × frequency) to gas flux for CMV and HFO. They tested the hypothesis that the distribution of ventilation during HFO may be less dependent on regional compliance[34] (as the RC model of Otis would suggest). After injecting Xe into the right atrium of the apnoeic dog – thus establishing a vertical gradient of Xe in the alveoli – they moved the dog to the prone position. HFO was then initiated. The resulting regional clearances were found dependent on concentration of Xe and not topographical location, confirming their hypothesis.

The uniform distribution of ventilation during HFO in the presence of gravity dependent distribution of perfusion may be expected to increase V/Q mismatch except for a second phenomenon they demonstrated during HFO – inter-regional mixing[34] (Fig. 4). After right atrial injection of ^{133}Xe the Xe was distributed preferentially to dependent lung regions. With the onset of ventilation Xe cleared rapidly from dependent regions but concentration rose transiently before falling in non-dependent regions – this reflected inter-regional mixing. Differences in mechanical properties of different lung regions causing asynchronous filling and emptying (pendelluft) may significantly contribute to this mixing. By making the composition of deadspace gas more homogeneous throughout the lung inter-regional mixing would lead to more uniformity of alveolar gas tensions. If it was of sufficient magnitude it may completely abolish the V/Q differences which would otherwise exist secondary to the uniform distribution of longitudinal (airway to alveolus) (Fig. 4) ventilation induced by HFO. Further studies by this group have found that the regional distribution of V/Q and efficiency of oxygenation were similar during CMV and HFO (at 15 and 20 Hz).[62] This suggests that, although inter-regional mixing does decrease the regional V/Q differences that would otherwise exist during HFO, it is not of sufficient magnitude to completely abolish them.

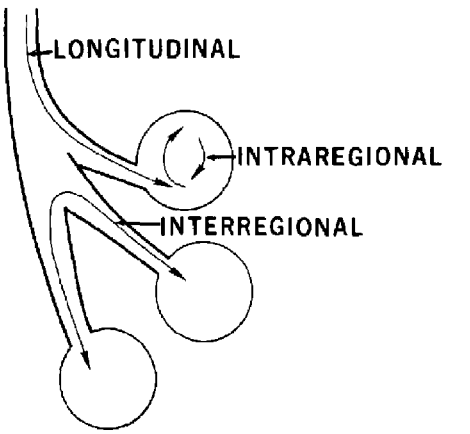

FIGURE 4 The three orders of transport operative during HFO: longitudinal, inter-regional mixing, and intra-regional mixing.

Gas exchange during HFO at 20 Hz has also been

studied with the inert gas exchange technique by McEvoy *et al.*[33] Their studies revealed a bimodal distribution with one peak centred on a V/Q of 1.0, the other at a higher V/Q – the latter peak was found an artifact due to enhanced transport of high solubility gases along the conducting airways.

The impact of the different distribution of ventilation on gas exchange in the diseased lung is not known. In chronic lung disease where gas exchange impairment is primarily due to V/Q mismatch rather than absolute shunt the inter- and intra-regional mixing, if of sufficient magnitude, may improve oxygenation, but no data are available. Crawford[36] has studied the effects of HFO (12–18 Hz) on oxygenation during anaesthesia. They found that in anaesthetized man impaired oxygenation, which is presumably due to increased shunting, is not improved by HFO. In those lung diseases characterized by absolute shunt HFO cannot of itself reverse shunt, other strategies (see later) must be added to recruit lung volume.

Mucociliary clearance during HFO

At the time of preparation of this review only one study has been published regarding mucociliary clearance during HFO. Several aspects of mucociliary transport have been studied by McEvoy *et al.*[37] They deposited an aerosal of 99 mTc sulphur throughout the lung and followed its clearance over a four-hour period of either CMV or HFO. After four hours eight to ten per cent of the tracer had been cleared in the CMV dogs but none had been cleared in the HFO group. The authors concluded that transport of at least part of the mucus layer (i.e., to the depth penetrated by the Tc) was disturbed by HFO. The possibility that the decreased clearance was due to ciliary damage was studied by measuring the tracheal transport velocity of a bolus of tracer after the four-hour period of ventilation was completed. The velocities were similar after both CMV and HFO suggesting that if the cilia are affected adversely by HFO it is a functional rather than structural defect from which they recover quickly. Another group[38] has followed the movement of ^{125}I labelled resin exchange particles in the trachea and found that both HFO and CMV retarded transport, but that there was no difference between the two.

McEvoy also studied the movement of a bolus of tracer deposited on the posterior trachea during HFO. In five of six dogs they demonstrated retrograde movement of the isotope into more distal airways rather than the usual anterograde progression seen normally. This may occur due to the inter-action of the high velocity flows generated during HFO with the mucus (two-phase flow), i.e. a "reverse cough." Two-phase flow in the bronchial tree is affected by several variables.[39–40] Whether a bolus is moved will depend on its depth and physical properties as well as the velocity, frequency and pattern of the oscillations. Chang[61] has demonstrated *in vitro* that the rate of mucus transport during oscillatory flow is directly proportional to the ratio between peak inspiratory and peak expiratory flow velocities. It is not clear whether sufficient shear is generated in secretions with layer thickness and with physical properties found in the bronchial tree to cause retrograde movement during HFO.

The other interesting observation of this group was that large amounts of mucus were found in the trachea of oscillated animals. The explanation for this may be that mechanical agitation of major bronchi may stimulate mucosal gland secretion. Interestingly, gas exchange function was preserved despite the presence of these large amounts of mucus in the airway. Excess secretions have not been remarked upon by most groups doing HFO studies, but the authors suggest that this may be because humidified circuits are not used in most animal studies. Exactly which factors influence this secretion, i.e., species, humidity, temperature, volume or frequency of oscillation, as well as the temporal sequence of this secretion (i.e., does it occur only on initiation of HFO) need to be explored.

The large amounts of mucus combined with retrograde transport in the trachea secondary to high gas velocities may explain the impeded clearance noted by this group. Clearance might have been improved with suctioning.

McEvoy's study is important in pointing out the possible effects of HFO on various aspects of mucociliary clearance. The impact of the phenomena outlined in the clinical setting is not clear. We have not experienced problems with secretions in our patients and animals during HFO.

Surfactant function and lung stability

Ventilatory pattern may affect both the surfactant system of the lung and lung stability. The effect of HFO on surfactant has been studied both in normal cats and in premature primates. In the normal cats[42]

biochemical indices, surface balance measurements and PV curves showed no difference between either HFO or CMV with PEEP. As well, the amount of surfactant present as tubular myelin (a less useful form) was unchanged. Morphology as revealed by light or electron microscopy was no different after the two modes of ventilation. In the other study premature primates were studied for four hours.[43] No changes in total lung phospholipids (PL) or DPC, in airway lavage PL, or ratio of airway lavage to total lung PL was observed. Postmortem PV curves were not different after CMV or HFO. These studies suggest that surfactant dynamics are not adversely affected by HFO. It is still an open question whether in cases of severe surfactant deficiency, as is present in ARDS of the newborn, large volume excursions are important to surfactant dynamics; since large breaths have been demonstrated to increase the amount of surfactant in the airways secondary to more rapid secretion by alveolar type II cells and to transfer of surfactant from the tubular myelin to the mono-molecular, surface active, phase.[41]

During CMV there is a progressive decrease in dynamic compliance with time. This may be related to micro atelectasis, increases in surface or tissue forces, or increases in smooth muscle tone.[63] Weinmann *et al.*[63] have compared CMV ($15\ ml \cdot kg^{-1}$, zero PEEP and 5 cm PEEP) with HFO (15 Hz) at matched pleural pressures. They found that the time course of the falls in dynamic compliance were similar with the two modes of ventilation.

Lung fluid balance

The lymph vessels of the lung possess valves, and the question of whether lung inflation propels lymph out of the lung through this valved system was studied by Drinker. He concluded that inflation did promote the transfer of lymph. With HFO, large phasic respirations are absent, and the question of whether this affects lymph transport and lung water arises. In cats ventilated with HFO for four hours, no increase in lung water determined from wet/dry ratios was found.[42] In sheep, with chronic lymph fistulas, Jeffries *et al.*[44] found that lung lymphatic function was not impaired by two to four hours of HFO even when lymph flow was augmented by the infusion of air microemboli. They concluded that whereas respiratory movements may transiently affect lymph flow they are not required for normal flow of lymph.

In a study of newborn lambs, decreased lymph flow, but no change in wet/dry weights of the lungs, was found when HFO was compared with CMV both in normals and in a group of animals where left atrial pressure had been increased for eight hours by inflation of a balloon.[45] The intrathoracic pressure was surprisingly high during HFO in this study and may have affected their findings. The effect of HFO on lung water in more severe models of acute lung disease or for more prolonged periods has not been studied.

Cardiovascular effects

It was hoped that HFO may have a cardiovascular sparing effect compared to more orthodox patterns of ventilation. Studies by Thompson *et al.*[46] in an oleic acid induced lung injury model did not demonstrate any difference in cardiac output when the dogs were ventilated with either CMV or HFO at equivalent MAP's. Sandoval[47] has demonstrated cardiac outputs 10–20 per cent higher during HFO than during CMV in a similar model. Studies in humans have revealed either no change (in paediatric patients post cardiac surgery)[48] or slight increases of 10–20 per cent in cardiac output (in adult ICU patients)[49] when HFO was substituted for CMV.

Haemodynamics and regional blood flow have been compared in the normal dog during CMV and HFO (20 Hz).[50] Animals were studied at both high and low airway pressures. No differences were found between the two modes of ventilation either in overall haemodynamics, intracranial pressure, or regional blood flow (as determined by the radiolabelled microsphere technique). Both modes of ventilation caused a depression of cardiac output and decreased splanchnic blood flow at the higher airway pressure. Thus currently studied models of acute lung injury and limited patient data suggest that MAP rather than ventilatory pattern determines cardiac output, there being little difference in CO when CMV and HFO are compared at equivalent MAP.

Metabolic functions of the lung

In recent years the importance of the lung as a metabolic organ has been realized. An effect of HFO on at least one of these metabolic functions has been demonstrated by Wetzel *et al.*[51] Mechanical deformation of the pulmonary vasculature generated by lung inflation has been shown to release

prostacyclin (PGI_2) from the pulmonary vasculature. PGI_2 is a potent pulmonary vasodilator and inhibits the pulmonary vascular response to hypoxia (HPV). They found that in isolated, perfused sheep lungs HFO increased the release of PGI_2 when compared to CMV. In the hypoxic lung the increased release of PGI_2 during HFO resulted in falls in pulmonary vascular resistance when compared to CMV, presumably by inhibiting HPV. Whether these findings apply to the intact animal will have to wait for the appropriate studies – the dynamics of lung distortion may be quite different in the intact thorax than in the isolated perfused preparation. The effects of HFO on other metabolic functions of the lung are unknown.

Studies in models of acute lung disease

HFO has been studied in several animal models of acute pulmonary insufficiency. Thompson[46] demonstrated that with oleic acid induced pulmonary oedema in dogs, when CMV and HFO were compared at equivalent mean airway pressures oxygenation and cardiac output were the same. This contrasts with our studies in rabbits in whom pulmonary damage was induced with either oleic acid or saline lung lavage.[32] We found that oxygenation was markedly better and lung volumes higher during HFO than during CMV at equivalent mean airway pressures. This was a consequence of the marked hysteresis of the lungs in these models which could be exploited by use of a sustained inflation at onset of oscillation (discussed later). Sznajder *et al.*[64] studied the impact of an inflation to total lung capacity during HFO in dogs with oleic acid induced pulmonary oedema. An inflation to TLC recruited lung volume and decreased shunt. Part of the volume recruited was rapidly lost but despite this the reduction in shunt persisted. They postulate that the portion of lung volume rapidly lost was that which had been recruited secondary to surface tension or tissue hysteresis. In contrast, that portion of the volume which had been recruited by redistribution of alveolar oedema was maintained (i.e., the alveoli did not become flooded again) and this was responsible for the continuing reduction in shunt.

Mayers *et al.* studied gas exchange in a combined broncho-pleural fistula and oleic acid lung injury model.[52] Because the distribution of ventilation becomes less dependent on regional compliance as frequency increases one might expect to lose a smaller fraction of the minute volume through the fistula (an infinite compliance) on HFO. With the fistula they found that (i) at the same mean airway pressure the leak rate on HFO was one-third that on CMV, and (ii) MAP could be adjusted independently of minute volume of ventilation, and thus PCO_2, on HFO but not CMV. With CMV they had difficulties with oxygenation because they were unable to generate a sufficiently high MAP to keep the damaged lung open. In contrast, with HFO they could increase the MAP by increasing fresh gas flow and thus maintain oxygenation.

Further studies in animal models of lung disease are needed to clarify the clinical indications for, and appropriate strategies to be employed during HFO.

Control of breathing

HFO has a profound effect on the control of breathing as in general spontaneous respiration ceases. At first this was thought to be similar to the apnoea that occurs during ECMO when CO_2 removal exactly matches CO_2 production. However, the apnoea during HFO is more complex as it also involves active inhibition of respiration. This inhibition occurs through at least two pathways. One pathway is certainly vagal.[57] During HFO there is significant volume change of the trachea and major airways, the site of the majority of the slowly adapting stretch receptors. From single fibre recordings it has been shown that there is an increase in stretch receptor discharge and an entrainment to the frequency of oscillation. Vagotomy usually abruptly terminates the apnoea, suggesting that oscillation is stimulating the slowly adapting receptors causing central inhibition. Not all animals start breathing after vagotomy and it has been suggested that there is a second inhibitory pathway from intercostal muscle spindles. Vibration of intercostal muscle spindles is known to inhibit respiration. Paralysis (with either polarising or non-depolarising agents) stimulates respiration as gauged by the return of phasic phrenic activity in a previously apnoeic animal.[53] The presumption is that paralysis abolishes intercostal spindle activity, the problem being that paralysis does a lot of other things at the same time. Other factors certainly influence this inhibition; it is, for example, impossible to inhibit breathing during oestrous. Of particular clinical importance is the effect of behavioural state on respiration during HFV. During the alert awake state respiration cannot be inhibited, although

some subjects can achieve very impressive breath-holding times.[54] In chronically tracheostomised dogs, trained to sleep in the laboratory during HFV, as soon as they become drowsy they become apnoeic or the respiratory rate is exceedingly slow and this continues throughout all NREM sleep.[55] However, when they enter REM sleep, irregular respiration starts interspersed with periods of apnoea, probably reflecting periods of phasic and tonic REM sleep. This escape from inhibition probably has three roots. (1) In REM (and the awake alert state) the Hering Breuer inflation reflex is practically abolished. (2) Spindle reflexes are abolished in REM. (3) During REM sleep the respiratory drive appears to be predominantly "behavioral" rather than metabolic, similar to the alert awake state. The clinical importance of this has become apparent using HFO in babies: if the infant is breathing and is not awake/alert or in REM sleep, there is something wrong with the ventilator or the infant.

Clinical use of HFO

While the physiological effects of HFO are becoming clearer, its clinical value as a life support device is not. There is fundamentally only one reason for utilizing HFO and that is the tidal volume is small. This *may* have two useful consequences. Small tidal volumes *may* reduce ventilator barotrauma. Small tidal volumes *may* alter the distribution of ventilation because the distribution becomes less dependent on regional compliance. How small should "small" be? As gas exchange is a function of fV^2 (at least in the normal dog lung) there is very little to be gained by going much higher than about 15 Hz and the volumes get rapidly larger below 15 Hz. If small volumes are the only issue, logic suggests that HFV should be run at somewhere around 15 Hz. Most of the clinical literature is from studies with jet ventilation at frequences of 4 Hz and below and there is very scanty literature on higher frequencies.

While the small tidal volumes may be the great advantage of HFO, they are also the greatest disadvantage. If all units in the lung are open, small tidal volumes will effect excellent gas exchange for both CO_2 and O_2. If there is extensive closure small tidal volumes will effect excellent CO_2 exchange through the open units, but poor O_2 exchange because the small volumes and pressures will not open closed units. The advantage of large volumes used during conventional ventilation is that sufficient pressure may be achieved to open closed units, the problem is in keeping them open in expiration.

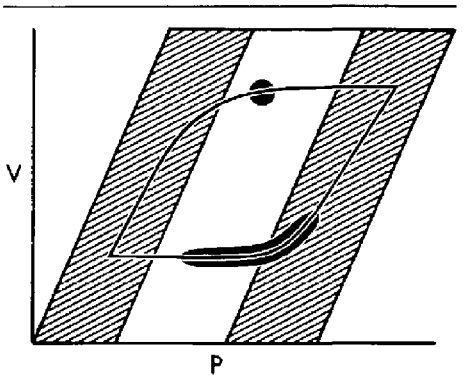

FIGURE 5 Hypothetical pressure–volume curve for the lung (see text).

This predicament is illustrated in Figure 5, which is a highly schematic representation of diseased lung. The PV curve is bounded by a band of opening pressures and at a lower pressure a band of closing pressures. Starting from some arbitrary end expired volume and pressure, there is no volume change until opening pressure is reached and then there is rapid recruitment of lung volume. During expiration there is a slow volume change until closing pressure is reached and then there is rapid derecruitment of lung volume. If the patient is then switched to HFO at the same MAP the oscillations are going into an atelectatic lung and generate fairly high pressures, but not high enough to recruit much lung volume and get effective O_2 exchange. One possible way to recruit volume is to inflate the lung to about 30–35 cmH_2O and hold this for a while to allow time-dependent recruitment and then drop the pressure to a pressure above closing pressure, so that the recruited volume is not lost.

This strategy works very well in some animal models of acute lung injury, producing excellent oxygen exchange and minimal barotrauma.[32,56] However, no human studies using this strategy have been reported. What the latter study also demonstated was the extensive hyaline membrane formation after a relatively short period of conventional mechanical ventilation. These changes decrease

lung compliance and probably increase both opening and closing pressures making it much more difficult to recruit and maintain lung volume on HFO. Thus the best effect of HFO should be seen when HFV is used *ab initio* whereas in the literature HFO has always been a relatively late intervention.

There is as yet no commercially available high frequency oscillator and the "home made" versions generally lack adequate safety devices which has impeded clinical trials; however, the National Heart Lung and Blood Institute are proposing a large collaborative trial on the use of HFO in the neonatal respiratory distress syndrome. This is an appropriate place to start for several reasons. IRDS is followed by a high (>15 per cent) incidence of chronic lung disease which is thought to be, at least in part, due to barotrauma. It has a single aetiology unlike ARDS which has multiple aetiologies and numerous entrained pathologies. However, the difficulties of studying even a "simple" model of human disease are considerable. Our experience is that some infants do remarkably well on HFO and others do not, and it is not clear whether this represents differences in the pathological process or subtle differences in our use of the device.

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References

1 NIH Report on High Frequency Ventilation, 1983 (to be published in AM Rev Respir Dis in 1984).

2 *Fredberg JJ.* Augmented diffusion in the airways can support pulmonary gas exchange. J Appl Physiol: Respir Environ Exercise Physiol 1980; 49: 232–8.

3 *Kamm RD, Slutsky AS, Drazen JM.* High-frequency ventilation. CRC Critical Reviews in Biomedical Engineering 1983; 9: 347.

4 *Chang HK.* Mechanisms of gas transport during ventilation by high-frequency oscillation. J Appl Physiol: Respirat Exercise Physiol 1984; 56: 553–63.

5 *Ross BB.* Influence of bronchial tree structure on ventilation in the dog's lung as inferred from measurements of a plastic cast. J Appl Physiol 1957; 10: 1–14.

6 *Slutsky AS, Drazen JM, Ingram RH Jr, et al.* Effective pulmonary ventilation with small-volume oscillations at high frequency. Science 1980; 209: 609–10.

7 *Mitzner W, Permutt S, Weinmann G.* A model of airway gas transport during high frequency ventilation. Ann Biomed Eng 1983; Vol II, Number 1.

8 *Scherer PW, Haselton FR.* Convective exchange in oscillatory flow through bronchial-tree models. J Appl Physiol: Respirat Environ Exercise Physiol 1982; 53: 1023–33.

9 *Knopp TJ, Kaethner T, Meyer M, Rehder K, Scheid P.* Gas mixing in the airways of dog lungs during high-frequency ventilation. J Appl Physiol: Respirat Environ Exercise Physiol 1983; 55: 1141–6.

10 *Solway J, Gavriely N, Kamm RD et al.* Intra-airway gas mixing during high-frequency ventilation. J Appl Physiol: Respirat Environ Exercise Physiol 1984; 56: 343–54.

11 *Scherer PW.* Gas transport in branched airways during high frequency ventilation. Ann Biomed Eng 1983; 2: 60–1.

12 *Tarbell JM, Ultman JS, Durlofsky L.* Oscillatory convective dispersion in a branching tube network. Transactions of the ASME, 1982; 104: 338.

13 *Collins J, Kamm RD, Shapiro AH, Drazen JM, Slutsky AS.* Measurements of gas transport in a branching network of tubes during oscillatory flow. Fed Proc 1983; 42: 1746.

14 *Isabey D, Harf A, Chang HK.* Alveolar ventilation during high-frequency oscillation: core dead space concept. J Appl Physiol: Respirat Environ Exercise Physiol 1984; 56: 700–7.

15 *Slutsky AS, Kamm RD, Rossing TH.* Effects of frequency, tidal volume, and lung volume on CO_2 elimination in dogs by high frequency. J Clin Invest 1981; 68: 1475–84.

16 *Fletcher PR, Epstein MA, Epstein RA.* A new ventilator for physiologic studies during high-frequency ventilation. Resp Physiol 1982; 47: 21–37.

17 *Jaeger MJ, Banner J, Gallagher J.* Alveolar ventilation in high frequency studies. (Abstract) Fed. Proc 1983; 42: 1351.

18 *Rossing TH, Slutsky AS, Lehr JL, Drinker PA, Kamm R, Drazen JM.* Tidal volume and frequency dependence on carbon dioxide elimination by high-

frequency ventilation. N Engl J Med 1981: 305: 1375.

19 *Goldstein D, Slutsky AS, Ingram RH, Westerman P, Venegas J, Drazen J.* CO_2 elimination by high frequency ventilation (4 to 10 Hz) in normal subjects. Am Rev Respir Dis 1981; 123: 251–5.

20 *Rossing TH, Slutsky AS, Ingram RH, Kamm RD, Shapiro AH, Drazen JM.* CO_2 elimination by high frequency oscillations in dogs: effects of histamine infusion. J Appl Physiol: Respirat Environ Exercise Physiol 1982; 53: 1256–62.

21 *Gavriely N, Solway J, Loring S, et al.* Airway dynamics during high frequency ventilation (HFV): A cineradiographic study. (Abstract) Physiologist 1982; 25: 282.

22 *Slutsky AS, Brown R, Lehr J, Rossing T, Drazen JM.* High frequency ventilation: A promising new approach to mechanical ventilation. Med Instrumentation 1981; 15: 229.

23 *Baum M, Benzer H, Goldschmied W, Mutz N.* Pressure flow pattern and gas transport using various types of high frequency ventilation. *In* P Scheck, UH Sjostrand and RB Smith (Eds), Perspectives in High Frequency Ventilation. The Hague Martinus Nijhoff, 1982.

24 *Thompson WK, Marchak BE, Froese A, Bryan AC.* High frequency oscillation compared with standard ventilation in pulmonary injury model. J Appl Physiol: Respirat Environ Exercise Physiol 1982; 52: 543–8.

25 *Soloway J, Gavriely N, Drazen JM et al.* Effect of bias flow rate on CO_2 removal during high frequency ventilation in human subjects. (Abstract) Fed Proc 25: 283.

26 *Otis AB, McKerrow CB, Bartlett A et al.* Mechanical factors in distribution of pulmonary ventilation. J Appl Physiol 1956; 8: 427–43.

27 *Lehr J.* Circulatory currents during high-frequency ventilation. (Abstract) Fed Froc 1980; 39: 576.

28 *Lehr J, Drazen JM, Zatz SL.* Regional expansion of excised dog lungs during high frequency ventilation. Fed Proc 41: 8639.

29 *Frank I, Noack PP, Lunkenheimer HI, et al.* Light and electron microscopic investigations of pulmonary tissue after high-frequency positive-pressure ventilation (HFPPV). Anaesthetist 1975; 24: 171.

30 *Simon B, Weinmann G, Mitzner W.* Significance of mean airway pressure during high frequency ventilation (HFV). Physiologist 1982; 25: 282.

31 *Vinegar A, Sinnett EE, Leigh DE.* Dynamic mechanisms determine functional residual capacity in mice, Mus musculus. J Appl Physiol: Respir Environ Exercise Physiol 1979; 46: 867–71.

32 *Kolton M, Cattran EB, Kent G, Volgyesi G, Froese AB, Bryan AC.* Oxygenation during high-frequency ventilation compared with conventional mechanical ventilation in two models of lung injury. Anesth Analg 1982; 61: 323.

33 *McEvoy RD, Davies NJH, Mannino FL et al.* Pulmonary gas exchange during high frequency ventilation. J Appl Physiol: Respirat Environ Exercise Physiology 1982; 52: 1278–87.

34 *Schmid ER, Knopp TJ, Rehder K.* Intrapulmonary gas transport and perfusion during high-frequency oscillation. J Appl Physiol: Respirat Environ Exercise Physiology 1981; 51(6): 1507–14.

35 *Brusasco V, Knopp TJ, Rehder K.* Gas transport during high-frequency ventilation. J Appl Physiol: Respirat Environ Exercise Physiol 1983; 55(2): 472–8.

36 *Crawford MR, Rehder K.* High frequency, small volume ventilation (HFO) in anesthetized man. Anesthesiology 1983; 59: A503.

37 *McEvoy RD, Davies NJH, Hedenstierna G, Hartman MT, Spragg RG, Wagner PD.* Lung mucociliary transport during high-frequency ventilation. Am Rev Respir Dis 1982; 126: 452–6.

38 *Armengol JA, Man SFP, Logus JW, Man GC, King EG.* Effects of high frequency ventilation on canine tracheal mucous transport. (Abstract) Crit Care Med 1981 (March): 192.

39 *Clarke SW, Jones JG, Oliver DR.* Resistance to two-phase gas–liquid flow in airways. J Appl Physiol 1970; 29: 464–71.

40 *King M, Chang HK, Weber ME.* Resistance of mucus-lined tubes to steady and oscillatory airflow. J Appl Physiol: Respirat Environ Exercise Physiol 1982; 52: 1172–6.

41 *Nicholas TE, Power JHT, Barr HA.* The pulmonary consequences of a deep breath: Respirat Physiol 1982; 49: 315–24.

42 *Frantz ID III, Stark AR, Davis JM, Davies P, Kitzmiller TJ.* High-frequency ventilation does not affect pulmonary surfactant, liquid, or morphologic features in normal cats. Am Rev Respir Dis 1982; 126: 909–13.

43 *Truog WE, Standaert TA, Murphy J, Palmer S, Woodrem DE, Hodson WA.* Effect of high frequency oscillation on gas exchange and pulmonary

phospholipids in experimental hyaline membrane disease. Am Rev Respir Dis 1983; 127: 585–9.

44 *Jefferies AL, Hamilton P, O'Brodovich HM.* Effect of high-frequency oscillation on lung lymph flow. J Appl Physiol: Respirat Environ Exercise Physiol 1983; 55: 1373–8.

45 *Raj JU, Goldberg RB, Bland RD.* Vibratory ventilation decreases filtration of fluid in the lungs of newborn lambs. Circ Res 1983; 53: 456–63.

46 *Thompson WK, Marchak BE, Froese AB, Bryan AC.* High-frequency oscillation compared with standard ventilation in pulmonary injury model. J Appl Physiol: Respirat Environ Exercise Physiol 1982; 52: 543–8.

47 *Sandoval J, Mayers I, Breen P, Oppenheimer L, Ali J, Wood LDH.* Relative effect of high frequency oscillatory ventilation (HFOV) and continuous positive pressure ventilation (CPPV) on hemodynamics, gas exchange and extravascular lung water (EVLW). (Abstract) Am Rev Resp Dis 1982; 4: 125.

48 *Vincent RN, Stark AR, Lang P, et al.* Hemodynamic response to high frequency ventilation in infants following cardiac surgery. Paediatric Res 1983; 17: 393A.

49 *Gillespie DJ.* High frequency ventilation: A new concept in mechanical ventilation. May Clin Proc 1983; 58: 187–96.

50 *Harris AP, Gioia FR, Traystman RJ, Rogers MC.* High-frequency ventilation: Hemodynamic responses at high airway pressure in dogs. Anesth Analg 1983; 62: 245–92.

51 *Wetzel RC, Gordon JB, Gregory T, Gioia FR, Sylvester JT.* High frequency ventilation attenuates the hypoxic pulmonary in isolated perfused sheep lungs. Anesthesiology 1983; 59: A499.

52 *Mayers I, Breen PH, Long GR, Wood LDH.* Canine bronchopleural fistula in low pressure pulmonary edema: high frequency oscillatory ventilation versus intermittent positive pressure ventilation. Am Rev Respir Dis 1983; 127(4): 103.

53 *England SJ, Onayemi A, Bryan AC.* Neuromuscular blockade enhances phrenic nerve activity during high frequency ventilation. J Appl Physiol: Respirat Environ Exercise Physiol 1984; 56: 31–4.

54 *Butler WJ, Bohr DJ, Bryan AC, Froese AB.* Ventilation by high frequency oscillation in humans. Anesth Analg 1980; 59: 577–84.

55 *England SJ, Sullivan C, Bowes G, Onayemi A, Bryan AC.* State related incidence of spontaneous breathing during high frequency ventilation. J Appl Physiol: Respirat Environ Exercise Physiol (in press 1984).

56 *Hamilton PP, Onayemi A, Smyth JB et al.* Comparison of conventional and high frequency ventilation: oxygenation and lung pathology. J Appl Physiol: Respirat Environ Exercise Physiol 1983; 55: 131–8.

57 *Thompson WK, Marchak BE, Bryan AE, Froese AB.* Vagotomy reverses apnea induced by high frequency oscillatory ventilation. J Appl Physiol: Respirat Environ Exercise Physiol 1981; 51: 1484–7.

58 *Boynton BR, Mannino FL, Meathe EA, Kopotic RJ, Friederichsen G.* Airway pressure measurement during high frequency oscillatory ventilation. Crit Care Med 1984; 12: 39.

59 *Allen J, Frantz I, Fredberg J.* Alveolar pressure distribution during high frequency oscillation: Effect of tidal volume. Fed Proc 1984; 43: 1301 (Abstract).

60 *Saari AF, Rossing TH, Solway J, Drazen JM.* Lung inflation during high-frequency ventilation. Am Rev Respir Dis 1984; 129: 333–6.

61 *Chang HK, King M, Weber ME.* Mucus transport by high frequency air oscillations with unequal peak inspiratory and expiratory velocities. Fed Proc 1984; 43: 121 (Abstract).

62 *Brusasco V, Knopp TJ, Schmid ER, Rehder K.* Ventilation-perfusion relationship during high-frequency ventilation. J Appl Physiol: Respirat Environ Physiol 1984; 56: 454–8.

63 *Weinmann GG, Brett AS, Mitzner W.* Lung compliance changes on high-frequency ventilation in normal dogs. J Appl Physiol: Respirat Environ Exercise Physiol 1984; 56: 506–12.

64 *Sznajder JI, Hansen DE, Long GR, Schumacker PT, Wood LDH.* Lung mechanics and O_2 exchange during HFOV in canine pulmonary edema. Fed Proc 1984; 43: 126 (Abstract).