Effect of I/E ratio on mean alveolar pressure during high-frequency oscillatory ventilation


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The possibility that gas trapping may occur during high-frequency oscillatory ventilation (HFOV) has been a source of concern for many years. This concern has been heightened by perceived similarities with conventional mechanical ventilation, where it is well recognized that gas trapping can occur at high ventilator rates (17, 18, 20).

During conventional mechanical ventilation (CMV), the time required for pressure to equilibrate between the alveolar space and the patient's airway, and thus for inspiration or expiration to be complete, is determined by the time constant, which is the product of compliance (C) and resistance (R) of the respiratory system. Because expiratory resistance is commonly up to fourfold greater than inspiratory resistance (17), application of rapid ventilator rates during CMV may easily compromise expiration. Gas trapping results, with elevation of alveolar pressure above airway pressure at end expiration, in a phenomenon commonly referred to as inadvertent positive end-expiratory pressure (3, 17, 20). To minimize the risk of this problem occurring during CMV at rapid rates, inspiratory-to-expiratory time (I/E) ratios of at least 1:2 are commonly employed.

Extrapolation of the principles underlying choice of I/E ratio for CMV has lead many authorities to also recommend the use of I/E ratios of at least 1:2 for HFOV, with the same intent of avoiding gas trapping and the associated dangers of hyperinflation, air leak, and cardiovascular compromise. The extent to which gas trapping occurs during HFOV, elevating mean alveolar pressure (P\text{A}) above mean airway opening pressure (P\text{ao}), remains controversial. Various investigators have reported that global or regional measures of P\text{A} may be the same (1, 5), higher (1, 2, 5, 7, 13, 19, 21), or lower (13, 25) than P\text{ao} during HFOV. Differences in ventilator settings including I/E ratio (13), P\text{ao} (5), ventilator amplitude (\Delta P\text{ao}) (1), and the effects of regional factors (1) and posture (1, 21) appear to account, at least in part, for these disparate observations.

To date, there has been no quantitative description of the effect of oscillatory ventilator settings and mechanical characteristics of the lung on the difference (P\text{diff}) between P\text{A} and P\text{ao}. This study was, therefore, undertaken to systematically examine the interaction of key ventilatory parameters on the magnitude of P\text{diff} in the lungs of young rabbits and in an in vitro lung model.

MATERIALS AND METHODS

Experiments were performed on the lungs of four adult rabbits and an in vitro model of the intubated newborn respiratory system. Animal experiments were performed in accordance with the guidelines of the Australian National Health and Medical Research Council and with the approval of the Animal Ethics Committees of Monash Medical Centre and Monash University (approval no. A9452).

Lung Models

Rabbit Lung Model. Four adult New Zealand White rabbits (body weight, 4.0 ± 1.8 kg) were administered a lethal dose of pentobarbital sodium (160 mg/kg) and intubated through a tracheostomy with an 11-cm-long, 3.0-mm-ID endotracheal tube (ETT) (Portex, UK). Intermittent positive pressure ventilation of the lungs (peak inspiratory pressure = 15 cmH\text{2}O; end-expiratory pressure = 5 cmH\text{2}O; rate = 30 breaths/min; and inspiratory time = 0.7 s) was initiated with a Humming II ventilator (Senko Medical Instrument Manufacturing, Japan) and maintained until the completion of surgical procedures when HFOV was commenced with a SensorMedics 3100 high-frequency oscillator. To measure alveolar pressure (P\text{A}) by the alveolar capsule technique (12, 13), a right thoracotomy was performed and a small plastic capsule glued (Supaglue, Selleys Chemical, Australia) to the exposed anterolateral surface of the right middle (n = 3) or
right lower (n = 1) lobe of the lung. The pleural surface enclosed within the capsule was punctured in five places with a 23-gauge needle inserted to a uniform depth (2 mm). The capsule opening was then sealed by inserting the tip of a Micron MP15 pressure transducer (Micron Instruments), which was carefully supported to exert minimal pressure on the underlying lung.

The capsule was confirmed to be free of leaks by demonstrating that PA remained constant after airway occlusion at end inspiration. Immediately before HFOV was commenced, the C and R of the respiratory system were determined by the airway-occlusion technique (16) by using a Hans Rudolph no. 1 pneumotachograph. Mean (± SD) C was 2.67 ± 0.64 ml/cmH2O, and mean R was 250 ± 0.13 cmH2O·s·l−1.

In vitro lung model. To simulate the mechanical properties of the respiratory system of the intubated human newborn infant suffering from hyaline membrane disease, we employed a lung model comprising an 11-cm-long, 3.0-mm-ID ETT, sealed into the neck of a 590-ml glass flask (see Fig. 1). The model had an adiabatic compliance C of 0.4 ml/cmH2O and an R of 75 cmH2O·s·l−1. [measured at a flow (V) = 0.1 l/s].

Measurement of Pressure

PA and pressure at the airway opening (Pao). Pao was measured with a Micron MP15 pressure transducer (Micron Instruments) via a sideport positioned immediately above the connection to the ETT and perpendicular to the ventilator tubing. Pressure in the interior of the in vitro lung model (PA) was also measured with an MP15 transducer positioned at the end of an 11-cm-long, 12-gauge needle inserted into the glass flask. Similar measurements of mean pressure were obtained when Pao was measured at other sites close to the airway opening and when PA was determined at a variety of sites within the glass flask (results not shown).

The time constant of the MP15 transducer response to a sudden change in pressure by balloon-burst testing was 0.7 ms for the MP15 transducer alone and 2.6 ms for the MP15-needle combination, indicating a frequency response that was adequate up to at least 454 and 134 Hz, respectively, for Pao and PA measurements. The output of the MP15 was linear over the range −70 to +140 cmH2O. Transducer signals were amplified and low-pass filtered at 400 Hz (Cyberamp 320, Axon Instruments), digitized at 1 kHz, and stored on a personal computer by using data-acquisition software (Spike2, Cambridge Electronic Design, UK).

Mean pressures. Measurements of mean pressures were determined from the average of at least 10 complete cycles of oscillation. The potential for errors arising from differences in transducer calibration when determining differences between PA and Pao was eliminated in the in vitro lung model by measuring PA and Pao with the same transducer connected either to the airway opening or to the interior of the lung. In the rabbit lung, each transducer was carefully calibrated to the same gain. Potential errors arising from zero drift were minimized by frequently referencing each transducer to the same static pressure, achieved by briefly reducing the amplitude of the pressure oscillation delivered by the high-frequency ventilator to zero.

Amplitude of pressure oscillation at the airway opening DPA. Reporting of the amplitude of pressure oscillation produced by the SensorMedics 3100 at the airway opening is confounded by the waveform's complex shape, which approximates to a square wave, upon which are superimposed large-amplitude, damped oscillations at the onset of both inspiration and expiration. Where observations were made at various amplitudes, we have reported the amplitude displayed by the ventilator. The ventilator internal pressure measurement provides a damped estimate of the amplitude DPA, since the pressure transducer is placed at the end of a 75-cm length of 3.5-mm-bore tubing attached to the inspiratory limb of the ventilator circuit, 1 cm before the patient's airway connection. Consequently, the DPA displayed by the ventilator approximates the amplitude of the square-wave component of the pressure waveform.

Calculation of tidal volume (VT) and V'. In the in vitro lung model, VT was calculated by using the equation

\[
VT = \frac{V_L \cdot \Delta PA}{\gamma \cdot P_0}
\]

where VL is model lung volume, ΔPA is amplitude of oscillatory pressure waveform in the model lung, P0 is atmospheric pressure, and γ is adiabatic gas constant (1.4 for air). V' was calculated throughout the oscillatory cycle by using numerical differentiation such that

\[
V' = C \cdot \frac{dPA}{dt}
\]

where C is model lung compliance and PA is the instantaneous pressure in the model lung.

Experimental Protocols

In all experiments, HFOV was delivered by a SensorMedics 3100 high-frequency oscillator, operated in accordance with the manufacturer's instructions. All observations were made at a mean airway pressure of 10 cmH2O.

Pdiff in the rabbit lung model. Experiments were performed to test whether significant differences between PA and
Pao could be identified in the rabbit lung model during HFOV and to investigate the effect of the I/E ratio on these differences. By using a ventilator frequency of 15 Hz, the magnitude of \( \Delta P_{\text{diff}} \) was determined at I/E ratios of 1:1 and 1:2 across a range of \( P_{\text{ao}} \) from a minimum of 10 cmH\(_2\)O to a maximum of 90 cmH\(_2\)O. Two observations were made at each setting, and average values of \( \Delta P_{\text{diff}} \) were determined for individual rabbits at each \( P_{\text{ao}} \) and I/E ratio.

\( \Delta P_{\text{diff}} \) in the in vitro lung model. Experiments were performed to test whether differences between \( P_{\text{a}} \) and \( P_{\text{ao}} \) could be identified in the in vitro lung model and to examine the independent effects of ventilator amplitude, frequency, and I/E ratio as well as the model lung compliance and ETT resistance on those differences. The range of ventilator settings examined and the characteristics of the lung model employed in each protocol are summarized in Table 1. Ventilator settings were changed in random sequence until triplicate observations of \( P_{\text{a}} \) and \( P_{\text{ao}} \) had been made under each experimental condition. Differences between \( P_{\text{a}} \) and \( P_{\text{ao}} \) were pooled to determine average values for \( \Delta P_{\text{diff}} \).

Statistical Analysis

Results are shown as means \( \pm \) SE. Statistical analysis of the data derived from the rabbit experiments was complicated by the unequal number of measurements of \( \Delta P_{\text{diff}} \) obtained across a range of ventilator amplitudes in each rabbit. A multilevel modeling approach using a nested hierarchical design was employed (statistical software MlN v 1.0a, Institute of Education, London, UK). Constant variance was assumed. Two levels were employed in the analysis to account for differences between the observations of \( \Delta P_{\text{diff}} \) made at different amplitudes (level 1) and between rabbits (level 2). Data at each I/E ratio were assessed separately.

RESULTS

\( \Delta P_{\text{diff}} \) in the Rabbit Lung

The measurements of \( \Delta P_{\text{diff}} \) made during HFOV in each of the rabbit lungs are illustrated in Fig. 2A. In the rabbit lung, \( \Delta P_{\text{diff}} \) was not significantly different from zero (maximum \( -0.8 \pm 0.3 \) cmH\(_2\)O) at an I/E ratio of 1:1. However, at an I/E ratio of 1:2, \( P_{\text{a}} \) was substantially less than \( P_{\text{ao}} \), and the magnitude of \( \Delta P_{\text{diff}} \) increased with the square of the oscillatory pressure amplitude at the patient’s airway to a maximum value of \( -5.0 \pm 0.2 \) cmH\(_2\)O.

\( \Delta P_{\text{diff}} \) in the In Vitro Lung Model

As in the rabbit lung, \( \Delta P_{\text{diff}} \) in the in vitro lung was \(< 1 \) cmH\(_2\)O at an I/E ratio of 1:1 (Fig. 2B). In contrast to the rabbit lung, however, \( \Delta P_{\text{diff}} \) was positive (\( P_{\text{a}} > P_{\text{ao}} \)), and a statistically significant difference in \( \Delta P_{\text{diff}} \) was demonstrable between models for amplitudes in excess of \( 30 \) cmH\(_2\)O. At an I/E ratio of 1:2, \( P_{\text{a}} \) was substantially less than \( P_{\text{ao}} \) (maximum difference \( -6.6 \pm 0.2 \) cmH\(_2\)O), and the difference increased with increasing amplitude in a similar manner to the rabbit lung.

Figure 3 illustrates the effect of changing the amplitude, frequency, and I/E ratio of the ventilator and both

\begin{table}
\centering
\caption{Ventilator settings and in vitro lung model characteristics}
\begin{tabular}{lcccc}
\hline
Protocol & Ventilator Settings & Lung Model \\
\hline
Effect of amplitude & 10–90* & 15 & 1:1, 1:2 & 0.4 & 3.0 \\
Effect of frequency & 10–90* & 7.5, 10, 15 & 1:2 & 0.4 & 2.5 \\
Effect of I/E ratio & 70† & 15 & 1:1–1:2.3‡ & 0.4 & 2.5, 3.0, 3.5 \\
Effect of ETT diameter & 10–90* & 15 & 1:2 & 0.4 & 0.1–2.0§ & 3.0 \\
Efficiency of compliance & 80 & 15 & 1:2 & \\
\hline
\end{tabular}
\end{table}

* Amplitude was adjusted in steps of 10–15 cmH\(_2\)O. † Amplitude was adjusted at each setting of inspiratory-to-expiratory time (I/E) ratio to deliver a calculated tidal volume of 7 ml. ‡ Inspiratory time, expressed as a percentage of total cycle time, was adjusted in steps of 2–3% between 30% (I/E = 1–2:3) and 50% (I/E = 1–1). § Compliance was varied by filling a 3.1-liter flask with measured volumes of water.
the ETT diameter and compliance of the lung model, on the magnitude of $P_{diff}$. An increase in ventilator frequency (Fig. 3A) at an I/E ratio of 1:2 or reduction of the inspiratory time as a fraction of total cycle time (Fig. 3B) caused $P_{A}$ to fall progressively below $P_{ao}$. Reduction in the resistance of the lung model, by increasing ETT diameter, decreased $P_{diff}$ at a given VT (Fig. 3C), whereas a change in compliance had negligible effect (Fig. 3D) until very low compliances were reached ($\leq 0.5 \text{ ml/cmH}_2\text{O}$), after which $P_{diff}$ fell rapidly with decreasing compliance.

DISCUSSION

In common with several previous publications (1, 6, 19, 21), we found evidence in this study that $P_{A}$ may differ significantly from $P_{ao}$ during HFOV and that I/E ratio is a crucial determinant of whether such a difference is present. The novel feature of our study is that it represents the first systematic evaluation of the effects of individual HFOV settings, and the influence of mechanical properties of the lung, on the magnitude of differences between $P_{A}$ and $P_{ao}$. We found no evidence of significant gas trapping ($P_{A} > P_{ao}$) at an I/E ratio of 1:1. Rather, differences between $P_{A}$ and $P_{ao}$ of sufficient magnitude to be of potential clinical significance ($\geq 1 \text{ cmH}_2\text{O}$) were seen only at an I/E ratio of 1:2 and were opposite in sign ($P_{A} < P_{ao}$). Interestingly, differences between $P_{A}$ and $P_{ao}$ (i.e., $P_{diff}$) could be elicited even in a very simple in vitro lung model, where their magnitude was very similar to that seen in whole rabbit lung oscillated at comparable settings, suggesting that the ETT itself is critical to the generation of $P_{diff}$.

Critique of Methods

Our in vitro and animal lung models were chosen because their mechanical properties resemble the human newborn infant’s respiratory system. Thus the compliance of the in vitro model (0.4 ml/cmH$_2$O) was comparable to that seen in severe hyaline membrane disease (13), a condition for which HFOV is commonly employed. We also used a range of ETTs (ID 2.5–3.5 mm) that spanned the range of sizes normally used for human newborn infants. However, although the total resistance of the intubated neonatal respiratory system has a significant contribution from the ETT (11), our in vitro model lacked conducting airways beyond the ETT, and its resistance must therefore have been less than that in the human newborn. Again, the rabbit was chosen as our whole lung model for its similarity in size.
Measurements of PA in the rabbit lung were made with the alveolar capsule technique, which has been used previously by several investigators to measure PA during high-frequency ventilation (1, 11–13). This technique has been demonstrated by Gerstmann and colleagues (13) to potentially overestimate PA when capsule and transducer are relatively heavy. We attempted to minimize this problem in our experiments by carefully supporting the pressure transducer to achieve a near-weightless condition. Whereas we cannot exclude the presence of some residual effect, we note that by causing overestimation of PA such an effect would have tended to lessen the Pdiff that we observed at an I/E ratio of 1:2. Employing a single alveolar capsule, we were unable to examine whether any regional variation in PA was present in our experiments. However, when regional variation is present, PA is usually lowest in the upper lobe of the lung during HFOV (1, 13), and our choice of the middle or lower lobe for alveolar capsule placement would again have tended to give a minimum estimate of the magnitude of the Pdiff present at an I/E ratio of 1:2.

Although measurement of static pressure is relatively uncomplicated, several investigators have previously noted that pressure measurements in a moving stream of gas may underestimate the driving pressure because of the Bernoulli effect (4, 8). In our measurement system, the most likely pressure to be affected by a Bernoulli effect was Pao; however, the worst-case calculated dynamic pressure at that site was <0.1 cmH2O.

Difference Between PA and Pao

In contrast to our finding of no more than small differences (<1 cmH2O) between PA and Pao in both the rabbit and in vitro lung models at an I/E ratio of 1:1, several previous studies in dogs (21), rabbits (13), and adult human subjects (19, 23) have each shown a potential for PA to be significantly elevated above Pao when HFOV was employed at an I/E ratio of 1:1. A number of mechanisms have been postulated to account for this effect, and each depends on the presence of asymmetry between inspiratory and expiratory resistance. They include changes in airway caliber between inspiration and expiration (15) that may be particularly evident at low lung volumes (low Pao) and the effects of flow separation at branch points in the airway (6). Bryan and Slutsky (5) have suggested, however, that the elevation of PA above Pao, observed in the study of Saari and colleagues (19) and that of Simon and co-workers (21), might alternatively be explained by the development of "choke points" that cause expiratory flow limitation at low Pao. In support of their hypothesis, they found the level of Pao to be the crucial determinant of whether gas trapping occurred in normal or surfactant-depleted rabbits given HFOV at an I/E ratio of 1:1.

The various potential sources of asymmetry between expiratory and inspiratory resistance (Re and Ri, respectively) outlined above each cause Re to exceed Ri, and, in turn, have the capacity to cause PA to exceed Pao. None, however, explains the observations made in our study where we saw minimal elevation of PA above Pao at a 1:1 ratio in the in vitro lung and no elevation at all in the rabbit lung, where such sources of asymmetry would have been most likely to be evident. The lack of evidence of PA exceeding Pao may well be explained by the observation made by Byran and Slutsky (5) that the level of Pao is a crucial determinant of whether gas trapping occurred in normal or surfactant-depleted rabbits given HFOV at an I/E ratio of 1:1. Our studies employed a Pao of 10 cmH2O, which is well above that employed in those earlier studies in which gas trapping was seen (1, 6, 17, 25, 28) but is no higher than the minimum Pao commonly employed in the clinical setting.

By contrast, the striking finding in our study was that, at an I/E ratio of 1:2, PA may fall substantially below Pao. Several years ago, Gerstmann et al. (13) made a similar observation that the average tracheal pressure may be less than Pao during HFOV in the rabbit at an I/E ratio of 1:2, and more recently Hatcher et al. (14) have found that PA determined by airway occlusion may be less than Pao at an I/E ratio of 1:2. The lower value of PA compared with Pao may again be accounted for by asymmetry between Re and Ri, but requires the unusual situation to arise, whereby Ri exceeds Re, which is the converse of the relationship when Pao is higher than Pao. Our data provide evidence that turbulence in the ETT, as first suggested by Gerstmann et al. (13), can account for this phenomenon.

Turbulence and Pdiff

During HFOV, one may predict that the high inspiratory and expiratory flows are likely to be associated with turbulence in the ETT. We may, therefore, expect that both the resistance R and the resistive pressure drop (Pres) along the ETT can be predicted from Rohrer's equation, such that R = k1 + k2V' and Pres = k1V' + k2V'2. If we assume that the values of k1 and k2 are similar in inspiration and expiration, we can then predict the effect of changes in inspiratory or expiratory flow V' on the magnitude of Pres during inspiration and expiration (see APPENDIX A).

In the simple circumstance of an I/E ratio of 1:1, the average inspiratory flow V'i must equal the average expiratory flow V'e, and both the resistance and Pres during inspiration and expiration will be equal. In our in vitro lung model at least, with no airways beyond the ETT, we would therefore expect PA to equal Pao. In contrast, at an I/E ratio of 1:2, the average inspiratory flow V'i must be twice the average expiratory flow V'e, since it is sustained for only half the time. As Pres depends on the square of V' under turbulent flow conditions, the average V'i2 will be four times greater than the average V'e2. The effect on Pres of doubling inspiratory flow with respect to expiratory flow will therefore exceed the countering effect on Pres of expiratory time doubling, relative to inspiratory time. Thus,
at an I/E ratio of 1:2, the unusual circumstance whereby \( R_i \) is greater than \( R_e \) arises, such that the inspiratory \( P_{res} \) must exceed the expiratory \( P_{res} \), with the inevitable consequence that \( P_{A} \) must fall below \( P_{A0} \) in our in vitro lung model. In more general terms, we can predict that, at any I/E ratio other than 1:1, \( P_{A} \) will deviate from \( P_{A0} \), and the magnitude of that deviation will be directly proportional to the difference between the mean squared inspiratory (\( U_i^2 \)) and expiratory velocities (\( U_e^2 \)) in the ETT (see Appendix A).

To test the capacity of this model to explain the magnitude of \( P_{diff} \) in our in vitro lung model, we have plotted each measurement of \( P_{diff} \) illustrated in Fig. 3 against the corresponding difference between \( U_i^2 \) and \( U_e^2 \), which we determined (knowing the in vitro lung compliance) by differentiating the pressure change within the flask (see Fig. 4). The correlation between \( P_{diff} \) and \( U_i^2 - U_e^2 \) was very close \( (r^2 = 0.95) \), suggesting that the effect of turbulence could largely account for the \( P_{diff} \) seen in our in vitro lung model. Furthermore, the close similarity between the results obtained in the in vitro lung model and those obtained in the rabbit strongly suggests that, even in the whole lung, events occurring in the ETT may be the principal determinant of differences between \( P_{A} \) and \( P_{A0} \).

In deriving the relationship between \( P_{diff} \) and \( U_i^2 - U_e^2 \), we have assumed that the values of \( k_1 \) and \( k_2 \) during inspiration are equal to those during expiration. Sly et al. (22) have published \( k_1 \) and \( k_2 \) values measured during steady flow for a number of ETT values ranging in size from 2.5 to 5.5 mm ID. Their observations suggest that \( k_1 \) and \( k_2 \) during expiration are slightly higher than during inspiration, by \(-10\%\), in agreement with differences in the inspiratory and expiratory ETT flow profiles observed by Chang and Mortola (9). Such a small increase of expiratory resistance relative to inspiratory resistance could account for the small elevation of \( P_{A} \) above \( P_{A0} \) in our in vitro lung model at an I/E ratio of 1:1. A further point of interest is that the calculated slope of the relationship between \( P_{diff} \) and \( U_i^2 - U_e^2 \) is \(-0.012\), which is in good agreement with the theoretically predicted slope \((-0.013) \) calculated from the experimental data of Sly et al. (22) (see Appendix A).

Clinical Implications

Although a substantial \( P_{diff} \) was only seen at relatively high ventilator pressure amplitudes in these experiments, it should be noted that the resistance of our in vitro lung model \((75 \text{ cmH}_2\text{O} \cdot \text{s} \cdot \text{l}^{-1})\) was relatively low, compared with established values of resistance in the intubated newborn infant with respiratory distress \((120–380 \text{ cmH}_2\text{O} \cdot \text{s} \cdot \text{l}^{-1}) \) (24). Given that our in vitro studies show that \( P_{diff} \) increases with increased airway resistance, it is likely that \( P_{diff} \) may reach substantial levels at lower pressure amplitudes when an I/E of 1:2 is used in the sick intubated newborn baby. Similarly, the resistance of the ETT itself may be higher in the clinical setting, where its interior is frequently coated with secretions. The development of high-frequency ventilators with a capacity to deliver I/E ratios of 1:3 or more further increases the possibility of substantial \( P_{diff} \) occurring even at relatively low amplitude.

Importantly, the pressure difference that arises across the ETT is a rapidly achieved, steady-state phenomenon. The main clinical consequence of this phenomenon, therefore, is that whenever the mechanical characteristics of the respiratory system or ventilator settings are altered, a new lung volume will result. The magnitude of such changes in lung volume will increase as I/E ratio moves away from 1:1. Our studies show that the adoption of I/E ratios approaching 1:1 might eliminate the fluctuations in lung volume, which might otherwise result from the pressure drop across the ETT. Where I/E ratios other than 1:1 are employed, the accurate measurement of flow across the ETT would provide a means of calculating the difference in mean pressure between the airway opening and the lung.

The optimization of lung volume has been a focus of clinical HFOV strategies during the last decade. Common clinical practice involves initial setting of \( P_{A0} \) 1–2 cmH\(_2\)O higher than that employed during CMV, with increments in \( P_{A0} \) being imposed until a substantial reduction in the inspired \( O_2 \) fraction, necessary to maintain normoxia, is achieved. To date, no data are available to indicate the extent to which the \( P_{A0} \) required in clinical practice for optimal lung recruitment may be related to the I/E ratio employed.
Although HFOV is frequently employed in the premature infant with hyaline membrane disease, which is a homogeneous lung disease, it is also used to ventilate neonates with other forms of respiratory disease. In some cases, this might be associated with a degree of ventilation inhomogeneity. Although it is likely that this scenario might create small regional differences in $P_A$, the pros and cons of a symmetric vs. asymmetric I/E ratio in the presence of conditions such as pulmonary interstitial emphysema remain to be tested.

In conclusion, our observations of minimal difference between $P_A$ and $P_{ao}$ at an I/E of 1:1, and the presence of a substantial difference at an I/E ratio of 1:2, call into question whether the common practice of employing an I/E ratio of 1:2 has the advantage of offsetting any effects on $P_{ao}$ amplitude and frequency, or in the size of the infant’s ETT, to have quite unanticipated and undesirable effects on $P_A$.

**APPENDIX A**

The instantaneous pressure at the airway opening $P_{ao}$ is equal to the sum of the resistive and inertive pressure drops associated with the ETT ($P_{res}$ and $P_{in}$, respectively) and the alveolar pressure $P_A$:

$$P_{ao} = P_{res} + P_{in} + P_A$$

(A1)

Integrating term by term over a full cycle and regrouping, we can write

$$P_A - P_{ao} = -(P_{res} + P_{in})$$

(A2)

(Note that in Eq. A2 and all that follow, the mean is taken over a complete cycle). Because $P_{in} = 0$ (see **APPENDIX B**), and defining $P_A - P_{ao} = P_{diff}$, Eq. A2 simplifies to

$$P_{diff} = -P_{res}$$

(A3)

When using Rohrer’s equation to represent the effects of turbulent flow in the ETT, the $P_{res}$ for inspiration (I) and expiration (E) is, respectively

$$P_{res,I} = k_{1I}V_{I}^1 + k_{2I}V_{I}^{1/2}$$

(A4a)

and

$$P_{res,E} = k_{1E}V_{E}^1 - k_{2E}V_{E}^{1/2}$$

(A4b)

where $V'$ is the flow in the ETT and $k_{1I}$, $k_{3I}$, $k_{1E}$, and $k_{2E}$ are experimentally determined constants. Note that the negative sign is necessary in Eq. A4b to take account of flow reversal during expiration. Recognizing that the $P_{res}$ over a complete cycle is

$$P_{res} = P_{res,I} + P_{res,E}$$

(A5)

and substituting Eq. A4a and A4b into Eq. A5 gives

$$P_{res} = k_{1I}V_{I}^1 - k_{2I}V_{I}^{1/2} + k_{1E}V_{E}^1 - k_{2E}V_{E}^{1/2}$$

(A6)

Assuming that $k_{1I} = k_{1E}$ and, further, that $k_{3I} = k_{2E} = k_2$, and recognizing that $V_{I}^1 - V_{E}^1$, Eqs. A3 and A6 yield

$$P_{diff} = -k_2(V_{I}^{1/2} - V_{E}^{1/2})$$

(A7)

Finally, rewriting Eq. A7 in terms of flow velocity $U$ in the ETT

$$P_{diff} = -k_2A^2(U_{I}^2 - U_{E}^2)$$

(A8)

where $A$ is the cross-sectional area of the ETT. Subject to the assumptions above, Eq. A8 indicates that the relationship between $P_{diff}$ and $U_{I}^2 - U_{E}^2$ is a straight line through the origin with a negative slope of $k_2A^2$. Calculation of $k_2A^2$, using averaged $k_2$ values derived from the inspiratory and expiratory data of Sly et al. (22) for a 10-cm-long ETT, gives $-0.014$, $-0.013$, and $-0.011$ for 2.5-, 3.0-, and 4.0-mm ETTs, respectively. The average calculated slope for the three ETTs is $-0.013$, in excellent agreement with that deduced from Fig. 4, which is $-0.012$.

**APPENDIX B**

The pressure drop $P_{in}$ across the inertance (I) of the ETT is

$$P_{in} = \int \frac{dV'}{dt}$$

(B1)

where $V'$ is the instantaneous flow in the ETT.

Assuming I is invariant, the average $P_{in}$ is, therefore

$$P_{in} = \frac{1}{T} \int_0^T \frac{dV'}{dt} dt$$

(B2)

where the integration is taken over a full cycle with duration $T$.

Evaluation of Eq. B2 gives

$$P_{in} = \frac{1}{T} [V'(T) - V'(0)]$$

(B3)

If flow is periodic, so that $V'(T) = V'(0)$, then

$$P_{in} = 0$$

(B4)

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