Mid-Frequency Ventilation: Unconventional Use of Conventional Mechanical Ventilation as a Lung-Protection Strategy

Eduardo Mireles-Cabodevila MD and Robert L Chatburn RRT-NPS FAARC

BACKGROUND: Studies have found that increasing the respiratory frequency during mechanical ventilation does not always improve alveolar minute ventilation and may cause air-trapping. OBJECTIVE: To investigate the theoretical and practical basis of higher-than-normal ventilation frequencies. METHODS: We used an interactive mathematical model of ventilator output during pressure-control ventilation to predict the frequency at which alveolar ventilation is maximized with the lowest tidal volume (V_T) for a given pressure. We then tested our predicted optimum frequencies and V_T values with various lung compliances and higher-than-normal frequencies, with a lung simulator and 5 mechanical ventilators (Dräger Evita XL, Hamilton Galileo, Puritan Bennett 840, Siemens Servo 300 and Servo-i). RESULTS: Compliances between 10 mL/cm H_2O and 42 mL/cm H_2O yielded V_T between 4.1 mL/kg (optimum frequency 75 cycles/min) and 6.0 mL/kg (optimum frequency 27 cycles/min). The intrinsic positive end-expiratory pressure at the optimum frequency was always less than 2 cm H_2O. All the ventilators except the Hamilton Galileo had an optimum frequency near 50 cycles/min, whereas the predicted optimum frequency was 60 cycles/min. CONCLUSIONS: With these ventilators and pressure-control ventilation, alveolar minute ventilation can be optimized with higher-than-normal frequency and lower V_T than is commonly used in patients with acute respiratory distress syndrome. We call this strategy mid-frequency ventilation. *Key words: mechanical ventilation, high-frequency ventilation, tidal volume, V_T, acute respiratory distress syndrome, acute lung injury*. [Respir Care 2008;53(12):1669–1677. © 2008 Daedalus Enterprises]

Introduction

Lower tidal volume (V_T of 6–8 mL/kg) is now the standard of care for acute lung injury/acute respiratory distress syndrome (ARDS)[1] and has been suggested for all patients on mechanical ventilation.[2] Lowering the V_T leads to increased respiratory frequency to compensate for lost alveolar minute volume ($\dot{V}_E$).[3] However, the respiratory frequency is typically limited to approximately 35 cycles/min because of concerns related to intrinsic positive end-expiratory pressure (auto-PEEP), gas exchange, and hemodynamic compromise,[4-7] so $\dot{V}_E$ is commonly limited to the product of a V_T of 6–8 mL/kg and a frequency of 35 cycles/min.[8,9]

See the Related Editorial on Page 1655

Recent studies of high ventilatory frequencies in patients with ARDS have had conflicting results. Two studies[10,11] found that increasing the frequency decreased the P_{aCO_2}, but auto-PEEP developed, including in a trial[7] where increasing the frequency with volume-control ventilation did not significantly reduce the P_{aCO_2} and caused hemodynamic compromise due to an increase in mean airway pressure ($\bar{P}_{aw}$). The differences in results can be explained by the ventilator strategies used, heterogeneous populations, methods of dealing with auto-PEEP, and instrument dead space (V_D). Hence, it seems premature to state that

Eduardo Mireles-Cabodevila MD and Robert L Chatburn RRT-NPS FAARC are affiliated with the Respiratory Institute, Cleveland Clinic, Cleveland, Ohio.

The authors report no conflicts of interest related to the content of this paper.

Correspondence: Robert L Chatburn RRT-NPS FAARC, Respiratory Therapy, M-56, Cleveland Clinic, 9500 Euclid Avenue, Cleveland OH 44195. E-mail: chatbur@ccf.org.

increasing the frequency in conventional mechanical ventilation is not an effective way to improve gas exchange.[7,12]

The relationship between frequency and $\dot{V}_E$ partly depends on the ventilation mode (volume control vs pressure control). This difference is explained by the determinants of V_T. In volume control the V_T is a set parameter. With pressure control the V_T (of a passive inspiration) is the result of the interaction between the change in airway pressure (end-inspiratory pressure minus end-expiratory transrespiratory system pressure), the time constant of the respiratory system, and the set inspiratory time.[13] When the respiratory system characteristics remain constant, the change in pressure difference and inspiratory time determine the V_T.

While keeping a constant duty cycle, increasing the frequency will have these effects:

1. In volume-control ventilation, the $\dot{V}_E$ and alveolar $\dot{V}_E$ increase linearly. The resultant decrease in expiratory time causes gas-trapping and a linear increase in auto-PEEP and $\bar{P}_{aw}$.

2. In pressure-control ventilation, V_T decreases due to shortened inspiratory time and auto-PEEP. However, the drop in volume is offset by the increase in frequency, so $\dot{V}_E$ increases asymptotically.[14] In contrast, because V_D remains relatively constant, alveolar volume decreases with frequency, and alveolar $\dot{V}_E$ reaches a maximum value at what we call the *optimum frequency*. Interestingly, although auto-PEEP develops, $\bar{P}_{aw}$ doesn't change.[14] These characteristics make pressure-control ventilation an attractive option to evaluate higher ventilatory frequencies with conventional mechanical ventilation. However, in 1993 Burke et al found that one of the best intensive-care ventilators at that time could not deliver pressures and volumes consistent with theoretical ideals.[15] To our knowledge, no further investigations of this sort have been attempted since.

We studied the theoretical and practical basis of using higher-than-normal frequencies with pressure-control ventilation in a simulated paralyzed patient with ARDS. In the first phase of the study we developed an interactive spreadsheet program in which we applied a mathematical model to predict ventilator output with given patient and ventilator variables. We used the mathematical model to predict the frequency that would maximize alveolar ventilation. In the second phase we used a lung model of a patient with ARDS and tested 5 mechanical ventilators at higher frequencies than are commonly used.

Methods

Phase 1: Mathematical Model

We used a validated mathematical model[14,15] to describe pressure-control continuous mandatory ventilation of a passive, single-compartment, lumped-parameter model. The equations in Table 1 include patient-determined and clinician-set variables, from which the ventilator output is obtained. The original equation for alveolar ventilation[14] was modified by making V_D a constant volume based on patient weight (rather than a fixed percentage). This modification resulted in an expression for alveolar ventilation that has a maximum value over a range of ventilator frequency from 1 to 150 cycles/min. For convenience, the model was designed to allow input of the V_D/V_T ratio rather than absolute values for V_D, because V_D/V_T can be easily evaluated at the bedside (eg, with a $NICO_2$ monitor, Respironics, Carlsbad, California). V_D is then calculated as the product of V_D/V_T, the patient's weight, and the V_T at which the V_D fraction was evaluated.[16] The required alveolar ventilation was estimated with the equations described by Laubscher et al.[17]

We programmed an interactive spreadsheet (Excel, Microsoft, Redmond, Washington) with the equations to plot $\dot{V}_E$, alveolar ventilation, $\bar{P}_{aw}$, and auto-PEEP as functions of ventilator frequency. The patient variables were selected to represent an adult patient with ARDS:[16,18,19] inspiratory resistance (R_I) 10 cm H_2O/L/s, expiratory resistance (R_E) 15 cm H_2O/L/s, V_D/V_T 0.5, compliance 0.020 L/cm H_2O, body weight = 66 kg.

The V_D was calculated as the product of V_D/V_T, body weight, and V_T (in mL/kg). For this baseline calculation

Table 1. Modeling Equations for Pressure-Control Ventilation

$$V_T = (P_{set} \times C)(1 - e^{-60D/fR_IC})(1 - e^{-60(1-D)fR_EC})/(1 - e^{-60(1-D)fR_EC} \times e^{-60D/fR_EC})$$

$$\dot{V}_E = f \times V_T$$

$$V_A = V_T - V_D$$

$$\dot{V}_A = f \times V_A$$

$$\text{auto-PEEP} = P_{set}(e^{-60(1-D)fR_EC})(1 - e^{-60D/fR_IC})/(1 - e^{-60(1-D)fR_EC} \times e^{-60D/fR_IC})$$

$$\bar{P}_{aw} = P_{set} \times D + PEEP$$

$$V_D = \frac{V_D}{V_T} \times V_T$$

$$\text{Required } \dot{V}_A = \frac{V_D \times 1.35}{0.05}$$

V_T = tidal volume
P_{set} = set pressure limit (cm H_2O above the set positive end-expiratory pressure)
C = compliance (L/cm H_2O)
e = Euler's constant (the base of natural logarithms; approximately 2.718)
D = duty cycle (ratio of inspiratory time to total respiratory cycle time)
f = ventilator frequency (cycles/min)
R_I = inspiratory resistance (cm H_2O/L/s)
R_E = expiratory resistance (cm H_2O/L/s)
$\dot{V}_E$ = minute volume
V_A = alveolar tidal volume (L)
V_D = dead space (L)
$\dot{V}_A$ = alveolar minute volume (L/min)
auto-PEEP = intrinsic positive end-expiratory pressure
$\bar{P}_{aw}$ = mean airway pressure.

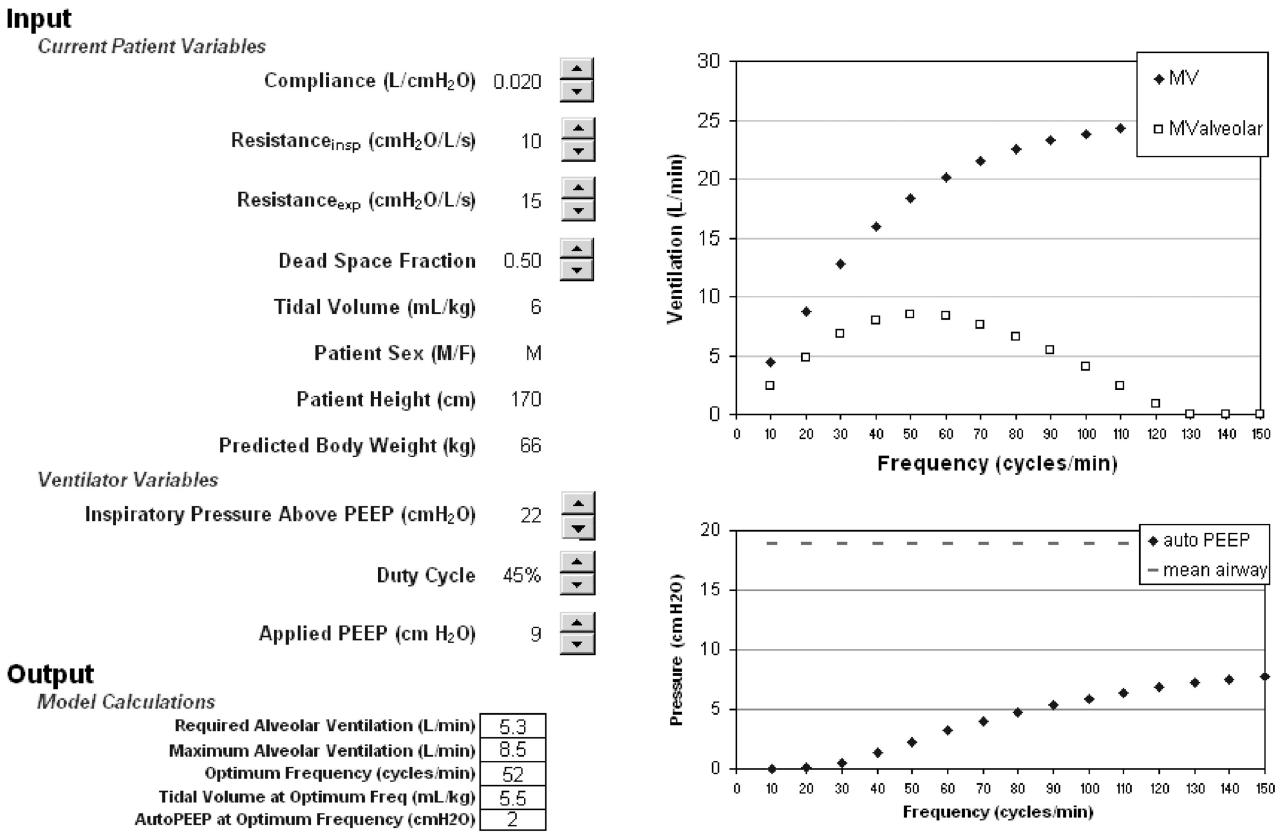

Fig. 1. Screen shot of the spreadsheet model, showing patient variables, ventilator settings, and output graphs. PEEP = positive end-expiratory pressure. MV = minute volume.

we assumed a V_T of 6 mL/kg, so V_D was assumed to be constant and V_D/V_T increased as the pressure-control V_T decreased.

Once the patient variables were determined, we set the ventilator variables as follows: The duty cycle was adjusted to 45%, to maximize volume delivery (optimal duty cycle). When $R_I = R_E$ the optimal duty cycle is 50%. When $R_I > R_E$ the optimal duty cycle is $> 50\%$, and vice versa if $R_I < R_E$.[14] PEEP was set at 9 cm H_2O, and the pressure limit above PEEP was adjusted to produce a $\dot{V}_E$ of approximately 13 L/min at a frequency of 30 cycles/min. These values were selected to match the average values in the ARDS Network study,[3] so that our first hypothesis could be tested with realistic values for alveolar ventilation, V_T, and optimum frequency.

Figure 1 shows an example of the model output, based on the lung mechanics and ventilator settings of a simulated patient with ARDS. Alveolar ventilation is maximized at a frequency of 52 cycles/min. The V_T calculated by the model (not shown in Table 1) was 6.4 mL/kg at 30 cycles/min, which was the average frequency used in the ARDS Network study.[3] The optimum frequency of 52 cycles/min yielded an alveolar ventilation of 8.5 L/min, but the required alveolar ventilation for this patient was only 5.3 L/min, so we reduced the inspiratory pressure above PEEP, which reduced the predicted optimum frequency. We considered the V_T calculated by the spreadsheet at the required alveolar $\dot{V}_E$ and new optimum frequency to be the *optimum tidal volume* (V_T). We repeated this procedure for a range of compliance settings: 0.15–0.63 mL/cm H_2O/kg (ie, 10–42 mL/cm H_2O for a simulated body weight of 66 kg), to match the average value in the ARDS Network study.[3]

Phase 2: Ventilator Performance

We used a high-fidelity servo lung simulator (ASL5000, IngMar Medical, Pittsburgh, Pennsylvania) to evaluate the relationship between frequency and alveolar $\dot{V}_E$ with 5 common intensive-care ventilators (Evita XL, Dräger, Lübeck, Germany; 840, Puritan Bennett/Tyco, Mansfield, Massachusetts; Galileo, Hamilton, Bonaduz, Switzerland; Servo-i, Siemens Elema, Solna, Sweden; and Servo 300, Siemens Elema, Solna Sweden) and compared the ventilators' performance to the theoretical results from the mathematical model. We directly measured and/or calculated the ventilator output. The lung simulator uses a computer to control the movement of a piston according to the equa-

tion of motion for the respiratory system. Constant compliance is simulated by moving the piston such that:

$$dV = dP \times C$$

where d is the derivative with respect to time (t), V is volume, P is pressure, and C is compliance. The constant resistance is calculated as:

$$R = \frac{dP}{dV/dt}$$

where R is resistance. So the piston is moved at a speed of:

$$dV/dt = dP/R$$

The lung simulator can also model non-constant resistance and compliance and patient ventilatory efforts (simple triggering efforts or full spontaneous breathing).

We set the lung simulator to model a passive respiratory system, composed of a single linear constant resistance and single constant compliance: $R_I = R_E = 10$ cm H_2O/L/s, and compliance of 0.025 L/cm H_2O. These parameters were kept constant during all the experiments. Data from the lung simulator were sampled at 500 Hz. Tidal volume was measured as the excursion of the piston inside the lung simulator (measured and displayed by the lung simulator's software). Alveolar volume was calculated as the V_T minus an assumed constant V_D of 150 mL.

Each ventilator was connected to the lung simulator via a conventional circuit (approximately 180 cm) with separate inspiratory and expiratory limbs (Airlife, Cardinal Health, McGaw Park, Illinois). We also attached an adult humidifier (MR250, Fisher & Paykel, Auckland, New Zealand) filled to the level line with unheated water. We used the same circuit for all the experiments. We calibrated and tested the ventilators for leaks prior to the experiments.

Experiment Protocol

All experiments were conducted with room air (fraction of inspired oxygen 0.21) and are reported as measured. The ventilator was set to deliver pressure-control continuous mandatory ventilation (ie, all breaths were time-triggered, pressure-limited, and time-cycled).

The mathematical model is based on a perfect square pressure waveform, so we set the ventilators to deliver as-perfect-as-possible square waveform (ie, minimum pressure rise time). The inspiratory pressure above PEEP (driving pressure) was set at 20 cm H_2O. No PEEP was applied (to avoid any interference from the exhalation manifold). The duty cycle was 50% (inspiratory-expiratory ratio 1:1) or as close as possible to 50% if the ventilator settings would not allow precisely 50%. The pressure rise time (if adjustable) and "plateau %" (explained below) were set to achieve an immediate rise to peak pressure. The ventilator frequency was increased in increments of 10 cycles/min, starting at 10 cycles/min, up to the maximum frequency achieved by the ventilator. Given the stability of the model, we report only one run for each experiment. After each incremental step we allowed 1 min to elapse before obtaining readings. Tidal volume, $\bar{P}_{aw}$, and auto-PEEP (after an expiratory pause of 2 s) were recorded from the lung simulator. We report the exhaled V_T because this was the output common to all the ventilators. Exhaled $\dot{V}_E$ and alveolar ventilation were calculated with the lung-simulator data.

Because no ventilator is expected to produce a mathematically perfect square pressure waveform, we defined the difference between the actual ventilator output and the theoretical output for V_T, $\bar{P}_{aw}$, and auto-PEEP as *performance error* (performance error = lung-simulator value minus value predicted by mathematical model). We obtained high-definition recordings of the $\bar{P}_{aw}$ tracings for comparative analysis.

Statistical Analysis

Continuous variables are reported as mean ± SD and minimum and maximum values, as appropriate. Group comparisons of quantitative variables are descriptive and graphed to represent the mathematical model and ventilator performance.

Results

Phase 1: Mathematical Model

Decreasing the inspiratory pressure with the lung parameters in Fig. 1 decreased the maximum alveolar ventilation to match the required alveolar ventilation calculated by the model, so the optimum frequency decreased to 45 cycles/min and optimum V_T was 4.8 mL/kg.

Using the procedure described in the methods section to adjust the spreadsheet model, and varying the compliance between 10 mL/cm H_2O and 42 mL/cm H_2O yielded V_T values between 4.1 mL/kg (optimum frequency 75 cycles/min) and 6.0 mL/kg (optimum frequency 27 cycles/min). At the optimum frequency, auto-PEEP was always < 2 cm H_2O.

Overall, the model behavior (in response to single changes in variables) can be summarized as follows. Increasing the compliance (by shifting the alveolar ventilation vs frequency curve to the left) increased the alveolar ventilation and reduced the optimum frequency. Decreasing the resistance or increasing the inspiratory pressure increased both the alveolar ventilation and the optimum

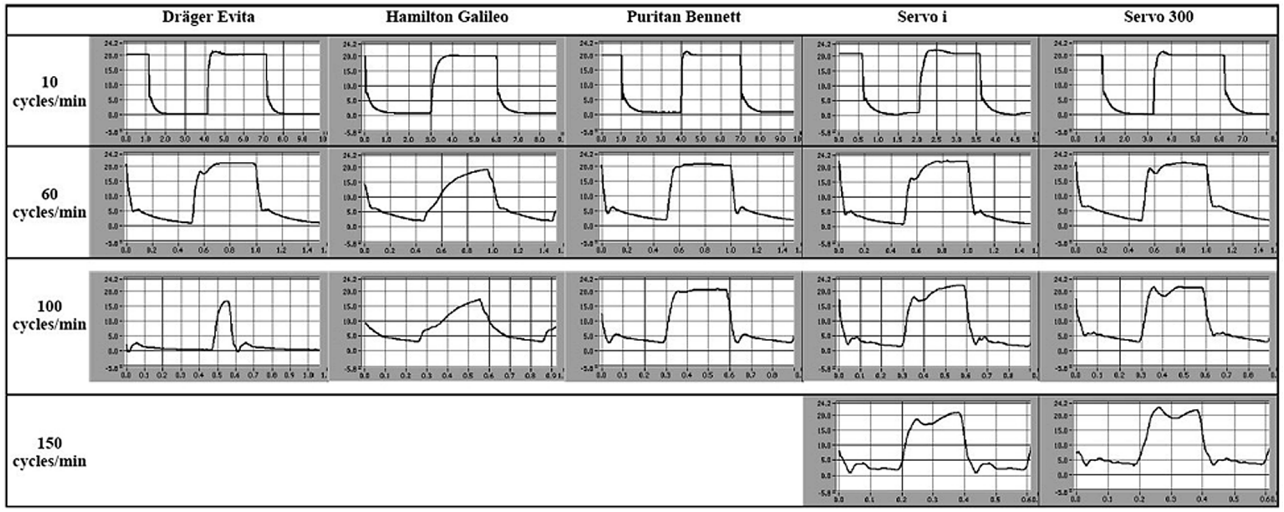

Fig. 2. Ventilator pressure waveforms from the lung simulator. The Evita XL, Galileo, and 840 ventilators could not be operated at 150 cycles/min. The Evita XL's waveform at 100 cycles/min is with a duty cycle of 0.20, because of limitations of the ventilator settings.

frequency. Changing the applied PEEP affected only the $\bar{P}_{aw}$. Changing the duty cycle in either direction away from 50% (inspiratory-expiratory ratio 1:1) decreased both the alveolar ventilation and the optimum frequency. When $R_I > R_E$ the optimal duty cycle is $> 50\%$, and vice versa: if $R_I < R_E$ the optimal duty cycle is $< 50\%$. Increasing the V_D decreased the optimum frequency. The interactive model is available on request to the authors.

Phase 2: Ventilator Performance

Figure 2 illustrates the pressure waveforms recorded by the lung simulator. The Galileo had the least square waveform (discussed below). The 840 had the squarest waveform (ie, best compared to the ideal step function of the mathematical model). The waveform from the Evita XL at 100 cycles/min represents a duty cycle of 0.20 because of its limited inspiratory-time settings at high frequency.

In addition to the clinician-set variables (PEEP, inspiratory pressure, frequency, and inspiratory-expiratory ratio), other variables inherent to each ventilator need to be adjusted to deliver the best waveform (Table 2). The Evita XL and the Servo-i have limited inspiratory-time settings, which altered the duty cycle at higher frequencies and account for the V_T differences (Fig. 3).

The "inspiratory rise time percent," "P-ramp (ms)," "plateau %," and "slope rise time" all refer to the speed to reach the plateau of the square waveform. The shortest rise time delivers the best waveform and the largest V_T. The shortest rise time on the Galileo is 50 ms, which causes the pressure waveform to lose its squareness and affects the V_T delivered. Interestingly, the 840 had the best square waveform with high demand settings (100 cycles/min), but was unable to deliver the predicted V_T because it produced less pressure-overshoot than the other ventilators. So the 840's better pressure control was a disadvantage in this context.

Ventilation Outcome Variables

Figure 3 shows the major outcome variable (alveolar ventilation as a function of frequency). With the exception of the Galileo, all the ventilators had an optimum frequency of about 50 cycles/min, whereas the predicted optimum frequency was 60 cycles/min. The Evita XL and Servo-i were the closest to the alveolar $\dot{V}_E$ predicted. The Galileo had an optimum frequency of 40 cycles/min because of its consistently lower V_T.

Figure 4 shows frequency versus auto-PEEP, $\bar{P}_{aw}$, and V_T. For V_T, the Evita XL's performance curve most closely followed the predicted curve up to 70 cycles/min. All the ventilators produced higher auto-PEEP and $\bar{P}_{aw}$ than predicted by the mathematical model, because airway pressure failed to drop immediately to baseline on exhalation. The effects of limited ventilator settings are seen in the data from the Evita XL and Servo-i at $>$ 70 cycles/min (inspiratory time limited), and with the Hamilton Galileo throughout (slow rise time).

As expected, none of the ventilators was able to perform overall as the mathematical model predicted (Table 3). However, the V_T delivered was within 10% of predicted up to frequencies of 30 cycles/min. Although the Evita XL and Servo-i continued to perform within 10% of predicted up to 70–90 cycles/min, this may be due to overshooting the set inspiratory pressure (see Fig. 2).

Table 2. Ventilator Characteristics in Mid-Frequency Ventilation

	Servo 300	Servo-i	Evita XL	840	Galileo
Frequency range (cycles/min)	0–150	0–150	0–100	0–100	0–120
Duty cycle adjustment	Set duty cycle; as rate changes T_I automatically changes	Set T_I and rate to keep the same duty cycle	Set T_I and rate to keep the same duty cycle	Set T_I and rate to keep the same duty cycle	Set duty cycle; as rate changes T_I automatically changes
Waveform settings	Inspiratory rise time set to minimum (0%)	Inspiratory time rise set to minimum (0)	Slope rise time set to minimum (0)	P% set to maximum (100%)	P-ramp set to minimum (50 ms)
Caveats	None	T_I has limited adjustment resolution, which alters the duty cycle at higher rates	T_I setting is limited above 60 cycles/min, altering the duty cycle.	None	Unable to achieve a square waveform

T_I = inspiratory time

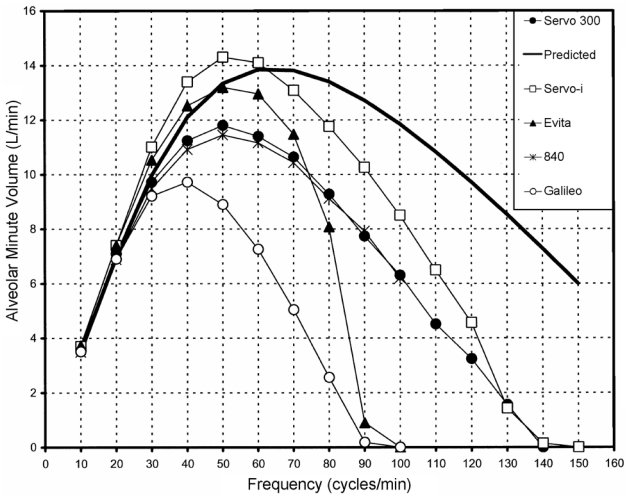

Fig. 3. Frequency versus alveolar minute volume.

Discussion

We have demonstrated, in a theoretical and physical model, that, during pressure-control ventilation at a constant duty cycle, increasing the frequency above commonly used frequencies might improve alveolar ventilation. Furthermore, we showed that we can achieve this with low V_T and a constant $\bar{P}_{aw}$. Interestingly, for many patients with relatively severe ARDS (ie, resistance $\leq$ 15 cm H_2O/L/s, compliance $\leq$ 35 mL/cm H_2O, and $V_D/V_T \leq 0.5$) the model predicts that maximum alveolar ventilation can be obtained with a $V_T < 6$ mL/kg at a frequency of > 35 cycles/min.

Most clinicians, we think, find the terms "high-frequency ventilation" and "conventional ventilation" of use in teaching and general communication about mechanical ventilation. The method we are proposing is neither. Thus, by referring to our proposed strategy as mid-frequency ven-

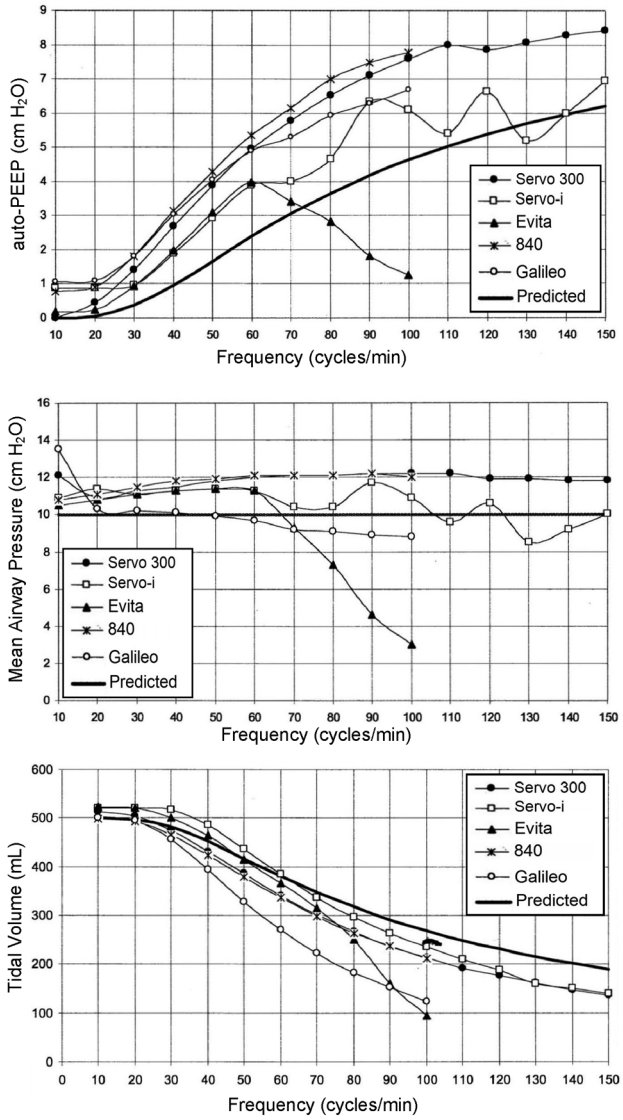

Fig. 4. Frequency versus intrinsic positive end-expiratory pressure (auto-PEEP), mean airway pressure, and tidal volume.

Table 3. Performance Error During Mid-Frequency Ventilation

	Performance Error*				
	Servo 300	Servo-i	Evita XL	840	Galileo
V_T (mean ± SD mL)	−28.8 ± 25.8	4.1 ± 25.4	9.5 ± 15.4	–34.5 ± 21	–83 ± 57
V_T range (mL)	–55 to 14	–33 to 35	–14.8 to 23	–56 to –1	–144 to 1
auto-PEEP (mean ± SD cm H_2O)	1.9 ± 1.1	1.2 ± 0.4	0.83 ± 0.6	2.4 ± 1	1.9 ± 0.5
$\bar{P}_{aw}$ (mean ± SD cm H_2O)	1.8 ± 0.4	1.1 ± 0.4	1.1 ± 0.3	1.8 ± 0.5	–0.03 ± 1.4

* Performance error = lung-simulator value minus value predicted by mathematical model
V_T = tidal volume
auto-PEEP = intrinsic positive end-expiratory pressure
$\bar{P}_{aw}$ = mean airway pressure

tilation we highlight the fact that conventional ventilators (not specialized high-frequency devices) can and possibly should be used at frequencies higher than the accepted normal range for patient size and also higher than commonly reported in sick ventilated patients. We are also pointing to a direction of inquiry that is diametrically opposed to the most popular ventilation mode today (volume control continuous mandatory ventilation, particularly in patients with ARDS).

The equation for alveolar ventilation described by Marini et al treated V_D as a fixed percentage of the V_T.[14] In contrast, we considered that for a real respiratory system, anatomic V_D is a (relatively) fixed value, so if V_T is $\leq V_D$, convective alveolar volume will be zero (discounting any of the putative gas-exchange mechanisms proposed for high-frequency ventilation).[20] It follows that if we consider

$$V_A = V_T - V_D$$

where V_D is assumed to be a fixed value,[21] the alveolar-ventilation-versus-frequency curve displays a peak rather than approaching an asymptote (see Fig. 1). The peak in alveolar ventilation corresponds to an optimum frequency and optimum V_T. Importantly, in pressure-control ventilation, as described by the mathematical model and confirmed in our experiment, the $\bar{P}_{aw}$ remained stable throughout the rise in frequency despite the frequency-dependent air-trapping (manifested as auto-PEEP). Indeed, auto-PEEP is predictable and can thus be quantitated nearly as accurately as externally applied PEEP.

A high ventilatory frequency with a conventional ventilator was initially examined while researching high-frequency positive-pressure ventilation, but was later abandoned for highly specialized ventilators.[22,23] There have been isolated reports and cases series that used prototypes[24] and adult[25] and neonatal ventilators.[26] Recently, Richecoeur et al[10] evaluated 6 patients with ARDS treated with a permissive hypercapnia strategy (by reducing V_T). Mechanical ventilation was optimized by increasing the frequency (from 18 ± 0 cycles/min to 30 ± 4 cycles/min) until auto-PEEP was detected. A significant reduction in P_{aCO_2} (from 84 ± 24 mm Hg to 60 ± 16 mm Hg) was observed.

Richard et al[11] described a P_{aCO_2} reduction from 61 ± 19 mm Hg to 43 ± 15 mm Hg after increasing the ventilator frequency from 17 ± 3 cycles/min to 30 ± 3 cycles/min, though this generated auto-PEEP (3.9 ± 1.1 cm H_2O). In contrast, Vieillard-Baron et al[7] did not find a difference in P_{aCO_2} (51 ± 7 mm Hg versus 47 ± 8 mm Hg) when they increased the frequency from 15 cycles/min to 30 cycles/min, and that strategy generated substantial auto-PEEP (6.4 ± 2.7 cm H_2O) and hemodynamic compromise. The differences in the results can be explained by differences in patient population, ventilator settings, and instrumental V_D.[27] All the trials used volume-control ventilation, which on its own seems unlikely to avoid the adverse effects of higher frequencies (see below). The only study that used pressure-control ventilation, by Paulson et al,[28] included 53 pediatric patients (mean age 4 y) with ARDS. They used a mean frequency of 80 cycles/min (range 40–120 cycles/min), low V_T (3–5 mL/kg), and high PEEP. Unfortunately, Paulson et al did not measure auto-PEEP, and no control group was reported.

There are several reasons for preferring pressure-control ventilation over volume-control ventilation at higher frequencies. The compliance of the patient circuit becomes a complicating factor in volume-control ventilation. Because the patient circuit compliance is in parallel with respiratory-system compliance, V_T is partitioned between the two. Prediction equations for volume control would have to include circuit compliance and would be more complicated. In contrast, with pressure control, compliances in parallel are exposed to the same pressure drop and hence the effect of patient circuit compliance is minimal so long as a square pressure waveform is maintained (which our results indicate is a reasonable assumption with some ventilators). Also, the higher the frequency, the shorter the

inspiratory time, and the higher the inspiratory flow must be for a given V_T. Pressure control (in general) produces higher peak flow than does volume control, and the flow is automatically adjusted to meet demand (ie, as respiratory system mechanics change), as opposed to volume control, which requires an arbitrary operator preset value.

Most ventilators can deliver adequate V_T at relatively high frequencies. Optimum ventilator performance (compared to the mathematical model) results from the ventilator's ability to deliver as square a pressure waveform as possible. The 3 determinants are: the ability to immediately rise to peak pressure; lack of oscillations in the plateau of the waveform; and the ability to immediately return to baseline pressure. Alterations in rise time and the plateau affect the V_T delivered. Alterations in expiration cause air-trapping and higher-than-predicted $\bar{P}_{aw}$ and auto-PEEP. Minimal changes to ventilator software (settings) and circuits (low V_D and compliance) should improve delivery of pressure-control ventilation at higher frequencies.

There are limitations to our mathematical model. Certain assumptions have to be made to derive the equations. We assumed a passive respiratory system (ie, to simulate a paralyzed patient). We assumed that inertance was negligible; however, as frequency increases, inertance may play a more important role. Inertance would decrease the V_T with a given inspiratory pressure limit and thus account for some of the difference between model predictions and ventilator performance.

Another limitation has to do with assumptions about V_D. Physiologic V_D changes with frequency,[29] V_T,[30] lung perfusion,[31] and instrumentation.[27,32] Furthermore, other factors make mathematical modeling very difficult, including the effects of mixing time in CO_2 removal,[33] other mechanism of gas exchange,[20] and pathology-specific V_D alterations.[16] Our model simply assumed a constant V_D calculated from the V_D/V_T (easily obtained at the bedside) at a given V_T and normalized for predicted body weight.[16]

The simplicity of our mathematical model, which considers a single unit with constant compliance and resistance, may seem an over-simplification of the lung. However, models as simple as this have been used previously[17] to calculate the behavior of the respiratory system, and were successfully implemented as ventilation modes.[34] Indeed, adaptive support ventilation (a pressure-control mode on Hamilton ventilators) uses the same assumptions as our model (ie, predicted V_D and $\dot{V}_E$ based on weight, and constant resistance and compliance). The difference is that adaptive support ventilation predicts optimum frequency and V_T based on minimizing the mechanical work of breathing, whereas our model for mid-frequency ventilation maximizes the alveolar $\dot{V}_E$.

The physical model of the respiratory system we used has the same limitations as the mathematical model. The ASL5000 lung simulator maintains resistance and compliance constant, which is a major difference from the study by Burke et al.[15]

Another limitation is the assumption of equal R_I and R_E in our ventilator experiments. It is more likely that expiratory resistance is greater than R_I, so the optimum frequency in terms of alveolar ventilation would be shifted downwards[35]. Nevertheless, our general results regarding these ventilators' ability to deliver higher frequencies still apply, with the understanding that clinical application would require bedside determination of both R_I and R_E.

Conclusions

With both a mathematical and a physical model we demonstrated the feasibility of predicting an optimal frequency and V_T based on maximizing alveolar $\dot{V}_E$ during pressure-control ventilation. V_T values determined in this way are lower and frequencies are higher than those reported in the literature for ventilating patients with ARDS. Our findings suggest that this approach may offer benefits, compared to conventional volume-control modes.

REFERENCES

1. Esteban A, Ferguson ND, Meade MO, Frutos-Vivar F, Apezteguia C, Brochard L, et al. Evolution of mechanical ventilation in response to clinical research. Am J Respir Crit Care Med 2008;177(2):170-177.
2. Schultz MJ, Haitsma JJ, Slutsky AS, Gajic O. What tidal volumes should be used in patients without acute lung injury? Anesthesiology 2007;106(6):1226-1231.
3. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342(18):1301-1308.
4. de Durante G, del Turco M, Rustichini L, Cosimini P, Giunta F, Hudson LD, et al. ARDSNet lower tidal volume ventilatory strategy may generate intrinsic positive end-expiratory pressure in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2002;165(9):1271-1274.
5. Bergman NA. Intrapulmonary gas trapping during mechanical ventilation at rapid frequencies. Anesthesiology 1972;37(6):626-633.
6. Hough CL, Kallet RH, Ranieri VM, Rubenfeld GD, Luce JM, Hudson LD. Intrinsic positive end-expiratory pressure in Acute Respiratory Distress Syndrome (ARDS) Network subjects. Crit Care Med 2005;33(3):527-532.
7. Vieillard-Baron A, Prin S, Augarde R, Desfonds P, Page B, Beauchet A, Jardin F. Increasing respiratory rate to improve CO_2 clearance during mechanical ventilation is not a panacea in acute respiratory failure. Crit Care Med 2002;30(7):1407-1412.
8. Meade MO, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Cooper DJ, et al. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA 2008;299(6):637-645.
9. Mercat A, Richard JC, Vielle B, Jaber S, Osman D, Diehl JL, et al. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA 2008;299(6):646-655.

10. Richecoeur J, Lu Q, Vieira SR, Puybasset L, Kalfon P, Coriat P, Rouby JJ. Expiratory washout versus optimization of mechanical ventilation during permissive hypercapnia in patients with severe acute respiratory distress syndrome. Am J Respir Crit Care Med 1999;160(1):77-85.
11. Richard JC, Brochard L, Breton L, Aboab J, Vandelet P, Tamion F, et al. Influence of respiratory rate on gas trapping during low volume ventilation of patients with acute lung injury. Intensive Care Med 2002;28(8):1078-1083.
12. Harrison BA, Murray MJ, Holets SR. All that's gold does not glitter: effects of an increase in respiratory rate on pulmonary mechanics and CO_2 kinetics in acute respiratory failure. Crit Care Med 2002; 30(7):1648-1649.
13. Marini JJ, Crooke PS, 3rd. A general mathematical model for respiratory dynamics relevant to the clinical setting. Am Rev Respir Dis 1993;147(1):14-24.
14. Marini JJ, Crooke PS 3rd, Truwit JD. Determinants and limits of pressure-preset ventilation: a mathematical model of pressure control. J Appl Physiol 1989;67(3):1081-1092.
15. Burke WC, Crooke PS 3rd, Marcy TW, Adams AB, Marini JJ. Comparison of mathematical and mechanical models of pressure-controlled ventilation. J Appl Physiol 1993;74(2):922-933.
16. Nuckton TJ, Alonso JA, Kallet RH, Danial BM, Pittet JF, Eisner MD, Matthay MA. Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. N Engl J Med 2002;346(17):1281-1286.
17. Laubscher TP, Frutiger A, Fanconi S, Jutzi H, Brunner JX. Automatic selection of tidal volume, respiratory frequency and minute ventilation in intubated ICU patients as start up procedure for closed-loop controlled ventilation. Int J Clin Monit Comput 1994;11(1):19-30.
18. Broseghini C, Brandolese R, Poggi R, Polese G, Manzin E, Milic-Emili J, Rossi A. Respiratory mechanics during the first day of mechanical ventilation in patients with pulmonary edema and chronic airway obstruction. Am Rev Respir Dis 1988;138(2):355-361.
19. Steinberg KP, Hudson LD, Goodman RB, Hough CL, Lanken PN, Hyzy R, et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med 2006;354(16): 1671-1684.
20. Chang HK. Mechanisms of gas transport during ventilation by high-frequency oscillation. J Appl Physiol 1984;56(3):553-563.
21. Radford EP Jr. Ventilation standards for use in artificial respiration. J Appl Physiol 1955;7(4):451-460.
22. Sjöstrand UH. In what respect does high frequency positive pressure ventilation differ from conventional ventilation? Acta Anaesthesiol Scand Suppl 1989;90:5-12.
23. Hess D, Mason S, Branson R. High-frequency ventilation design and equipment issues. Respir Care Clin N Am 2001;7(4):577-598.
24. El-Baz N, Faber LP, Doolas A. Combined high-frequency ventilation for management of terminal respiratory failure: a new technique. Anesth Analg 1983;62(1):39-49.
25. Flatau E, Barzilay E, Kaufmann N, Lev A, Ben-Ami M, Kohn D. Adult respiratory distress syndrome treated with high-frequency positive pressure ventilation. Isr J Med Sci 1981;17(6):453-456.
26. Boros SJ, Bing DR, Mammel MC, Hagen E, Gordon MJ. Using conventional infant ventilators at unconventional rates. Pediatrics 1984;74(4):487-492.
27. Prin S, Chergui K, Augarde R, Page B, Jardin F, Vieillard-Baron A. Ability and safety of a heated humidifier to control hypercapnic acidosis in severe ARDS. Intensive Care Med 2002;28(12):1756-1760.
28. Paulson TE, Spear RM, Silva PD, Peterson BM. High-frequency pressure-control ventilation with high positive end-expiratory pressure in children with acute respiratory distress syndrome. J Pediatr 1996;129(4):566-573.
29. Chakrabarti MK, Gordon G, Whitwam JG. Relationship between tidal volume and deadspace during high frequency ventilation. Br J Anaesth 1986;58(1):11-17.
30. Kiiski R, Takala J, Kari A, Milic-Emili J. Effect of tidal volume on gas exchange and oxygen transport in the adult respiratory distress syndrome. Am Rev Respir Dis 1992;146(5 Pt 1):1131-1135.
31. Kuwabara S, Duncalf D. Effect of anatomic shunt on physiologic deadspace-to-tidal volume ratio–a new equation. Anesthesiology 1969;31(6):575-577.
32. Hinkson CR, Benson MS, Stephens LM, Deem S. The effects of apparatus dead space on P_{aCO_2} in patients receiving lung-protective ventilation. Respir Care 2006;51(10):1140-1144.
33. Aboab J, Niklason L, Uttman L, Kouatchet A, Brochard L, Jonson B. CO_2 elimination at varying inspiratory pause in acute lung injury. Clin Physiol Funct Imaging 2007;27(1):2-6.
34. Arnal JM, Wysocki M, Nafati C, Donati S, Granier I, Corno G, Durand-Gasselin J. Automatic selection of breathing pattern using adaptive support ventilation. Intensive Care Med 2008;34(1):75-81.
35. Smith TC, Marini JJ. Impact of PEEP on lung mechanics and work of breathing in severe airflow obstruction. J Appl Physiol 1988; 65(4):1488-1499.