A Multi-segment Mathematical Model with Variable Compliance for Pressure Controlled Ventilation

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ABSTRACT: A mathematical model with multi-segment variable compliance which describes the volume of a single compartment lung for pressure controlled ventilation has been proposed and compared against a constant compliance model. The compliance in the constant compliance model is the average of those in the variable compliance model. In our model, on the other hand, a variable compliance is approximated by piecewise linear function of the lung volume. The model was then used to compute the outcome variables of clinical interest; tidal volume, average volume, end-expiratory pressure, and mean alveolar pressure. Using data obtained from healthy and injured pigs, the variable compliance model was used to study effects of recruitment maneuvers on the key outcome variables. Furthermore, the limiting value for each outcome variable was derived as a function of the physiologic and ventilatory parameters.

KEYWORDS: pressure controlled ventilation; mathematical model; multi-segment; variable compliance.

INTRODUCTION

Respiratory failure has become an important health problem, especially in a disease called acute respiratory distress syndrome (ARDS) which can harm and destroy the respiratory system. Many patients who suffer from this disorder need mechanical ventilation to aid breathing whenever they are not able to move enough air in and out of their lungs. Many types of ventilators and modes of operation may be used for the treatment. Pressure controlled ventilation is most often prescribed for patients with severe ARDS.1,2

The mechanism of respiration has gained increasing importance in the study of guidelines for ventilator settings in order to protect the lungs from damage. Many mathematical models for mechanical ventilation have been developed.3-10 The models are generally broken down into single compartment models and multi-compartment models. These models allow the resistances for inspiration and expiration to be different, incorporating positive end-expiratory pressure (PEEP), and covering the basic clinical modes of ventilation. However, most of these models have assumed the same constant compliance for the inspiratory and expiratory phases. The dynamics of the elastic pressure-volume ($P_e-V$) curves have also been studied extensively.11-16

Based on a study of Svantesson et al. in 1998,13 a three-segment variable compliance model for pressure controlled ventilation was proposed by Crooke et al. in 2002.17

Oleic acid-injured animal models are used widely to test a variety of adjunctive therapies in mechanical ventilation.18-20 Using animal models as a proxy for lung injury and disease, researchers have probed the effects of various therapeutic techniques, ranging from liquid ventilation,21 splanchnic perfusion and oxygenation,22 ventilatory support23-25 to tracheal gas insufflation (TGI).26 One of the more prominent usages of oleic acid-injury models is in studies of recruitment.23,27,28

The mathematical model developed in this paper is based on a subset of data collected from twenty pigs that were subjected to mechanical ventilation before and after oleic acid injury. The experimental protocol for the animal studies was approved by the Animal Care
and Use Committee of Regions Hospital. In order to study mechanical ventilation, the experiments were carried out by using monitoring equipments. The \((P_e,V)\) data was collected without applied positive end-expiratory pressure (PEEP = 0) during inspiration and expiration from pre- and post-injury pigs. The collected \((P_e,V)\) data for each pre- and post-injury pig showed that the injury has an effect on the lung compliance. Therefore, we constructed a multi-segment mathematical model for pressure controlled ventilation with variable compliance, based on a single compartment model. Using the experimental \((P_e,V)\) data from pre- and post-injury pigs, the lung’s variable compliance could be approximated by a piecewise linear function of the lung volume, \(V\). Next, this model was compared to a linear model with constant compliance of pressure controlled ventilation which served to link the clinical input variables, namely pressure level, frequency, inspiratory time fraction, and impedance, with key outcome variables of clinical interest, such as tidal volume, average volume, end-expiratory pressure, and mean alveolar pressure.

Furthermore, for traditional modes of ventilation, the tidal volume \((V_t)\), minute ventilation \((V_e)\), end-expiratory pressure \((P_e)\), mean alveolar pressure \((P_a)\), and power \((W)\) are asymptotic to finite limiting values as the cycling frequency \(f\) becomes sufficiently large.\(^5\) It is therefore informative to calculate these limiting values as \(f \rightarrow \infty\), in order to make some clinically relevant observations concerning these important key outcome variables. Such linkages between these key outcome variables \((V_t,V_e,P_e,P_a,W)\) and the physiologic variables (compliances and resistances) as \(f \rightarrow \infty\) will provide limits or bounds for these quantities, which can assist clinicians in the optimization of the desired outcomes on a particular clinical settings.

**Previous Model**

The mathematical model for pressure controlled ventilation incorporates pressure support ventilation that is applied to a single lung with compliance \(C\), inspiratory resistance \(R_i\), and expiratory resistance \(R_e\). The ventilator cycle is split into two parts: inspiration of duration \(t_i\) and expiration of duration \(t_e\). The total length of each cycle is \(t = t_i + t_e\).

One compartment models for mechanical ventilation are formed by assuming a pressure balance within the compartment:

\[
P_i + P_i + P_e = P_{vent}
\]

in which the pressure balance at any time \(t\) during each period of breathing cycle is composed of pressures due to resistive losses \((P_i)\), pressures due to elastic forces \((P_i)\), residual pressures \((P_{res})\), and applied pressures to the compartment \((P_{vent})\). During inspiration, a pressure \(P_{vent}\) is applied to the airway, \(P_{vent} = P_{set}\), and during expiration, the ventilator applies a constant pressure \(P_{vent} = P_{PEEP}\).

In actual fact, the lungs cannot be emptied of gas, even by the most forceful expiration. Some gas still remains as the residual volume. We define the end-expiratory volume \((V_e)\) to be the volume of the lung above its residual volume during a maximal forced expiration that starts at the end of a normal tidal expiration. \(V(t)\) denotes the volume of the compartment above \(V_e\) at any time \(t\). During each breathing cycle, \(V(t)\) and \(V_e(t)\) denote the volumes of the compartment above its residual volume during inspiration and expiration, respectively. We then assume that

\[
P_e = \frac{V}{C(V + V_e)}
\]

where \(C(V + V_e)\) is the compliance function for the elastic pressure. The residual pressure called the end-expiratory pressure, \(P_{res}\), is the pressure due to \(V_{res}\). The relationship between \(V_e\) and \(P_{res}\) is given by

\[
P_{res} = \frac{V_{res}}{C(V_{res})}.
\]

For the resistive pressure, we assume that

\[
P = R Q,
\]

where \(Q\) is the flow into or out of the lung, that is,

\[
Q = \frac{d V}{d t}.
\]

\(R\) is a constant, and \(\varepsilon\) is a positive parameter. With these assumptions, the volume of the compartment is given by the following differential equations.

**Inspiration**

\[
R \left( \frac{d V_i}{d t} \right) + \frac{V_i}{C(V_i + V_e)} + P_e = P_{set}, \quad 0 \leq t \leq t_i
\]

**Expiration**

\[
-R_e \left( \frac{d V_e}{d t} \right) + \frac{V_e}{C(V_e + V_{res})} + P_{res} = P_{PEEP}, \quad t_i < t \leq t_{tot}.
\]
(3), with constant compliance and \( \varepsilon = \varepsilon_c = \frac{1}{2} \) or 2, were found by Crooke and Marini in 1993. Most other researchers put \( \varepsilon = \varepsilon_c = 1 \) finding that their models work reasonably well and are more mathematically tractable. In 2002, Crooke et al. proposed, solved and analyzed a one-segment mathematical model for pressure controlled ventilation with variable compliance. Their one-segment model is of the form given in equations (2) and (3), when \( \varepsilon_c = \varepsilon_c = 1 \),

\[
C_i(V_i + V_{ex}) = a_i + b_i(V_i + V_{ex}),
\]

and

\[
C_e(V_e + V_{ex}) = a_e + b_e(V_e + V_{ex}),
\]

where \( a_i, b_i, a_e, b_e \) are parameters obtained from \( P_{d-V} \) the curves. That is,

**Inspiration**

\[
R_i \left( \frac{dV_i}{dt} \right) + \frac{V_i}{a_i + b_i(V_i + V_{ex})} + P_{es} = P_{set}, \quad 0 \leq t \leq t_{ins}
\]

**Expiration**

\[
R_e \left( \frac{dV_e}{dt} \right) + \frac{V_e}{a_e + b_e(V_e + V_{ex})} + P_{es} = P_{peep}, \quad t_{ins} < t \leq t_{tot}.
\]

### Multi-Segment Model

In 2002, Crooke et al. suggested a nonlinear mathematical model for pressure controlled ventilation called the three-segment model, in which the compliance of the compartment was allowed to be a piecewise linear function that varies with the compartment volume. Their compliance for each phase of breathing cycle was segmented into three parts, each of which varied linearly with volume up to a particular lung volume. In this paper, we attempt to improve the accuracy by proposing a multi-segment model in which the compliance for each part of the breathing cycle consists of multiple segments.

First, we consider the elastic pressure in the lung in its simplest form, that is

\[
P_{el} = \frac{V}{C(V)}
\]

where \( P_{el} \) is the elastic pressure of a single compartment lung and \( V \) is the lung volume above its residual volume. The experimental \( P_{d-V} \) data for inspiration and expiration, pre- and post-injury pigs applied in this paper was collected without applied PEEP and the end-expiratory pressure, \( P_{es} \), of the lung was assumed to be zero. Then, the function \( C(V) \), the compliance function of the model, is allowed to be a piecewise linear function over the inspiratory and expiratory phases for each breath. In particular, the compliance functions for inspiration \( C_i(V) \) and expiration \( C_e(V) \) of the multi-segment model, with \( f \) segments during inspiration and \( K \) segments during expiration, have the forms:

**Inspiration**

\[
C_i(V) = \begin{cases} 
  a_i + b_i V & \text{if } 0 \leq V \leq V_{i1} \\
  a_{i2} + b_i V & \text{if } V_{i1} \leq V \leq V_{i2} \\
  \vdots \\
  a_i + b_i V & \text{if } V_{i(f-1)} \leq V \leq V_i 
\end{cases}
\]

**Expiration**

\[
C_e(V) = \begin{cases} 
  a_{e1} + b_e V & \text{if } 0 \leq V \leq V_{e1} \\
  a_{e(k-1)} + b_e V & \text{if } V_{e1} \leq V \leq V_{e(k-2)} \\
  \vdots \\
  a_{ek} + b_e V & \text{if } V_{e1} \leq V \leq V_e 
\end{cases}
\]

where \( V_i \) and \( V_{ei} \) denote the volumes at which the compliance function changes its form during inspiration and expiration, respectively. The constants \( V_j \) and \( V_{ej} \), where \( j = 1, 2, \ldots, J \) and \( k = 1, 2, \ldots, K \), as well as the numbers \( J \) and \( K \) are determined as those which yield the least-squares fitting of the collected \( P_{d-V} \) data.

Thus, the multi-segment approximation of the compliance functions as in equations (7) and (8) is used in order to obtain a more accurate fit. To test the accuracy of our model, a Mathematica program was written to accept the experimental \( P_{d-V} \) data and obtained a least-squares fit of the experimental data up to 5 segments in each part of the breathing cycle. The resulting curves are shown in Fig 1 for both pre- and post-injury cases of a particular pig. The parameters used in a five-segment fit of \( P_{d-V} \) curves in Fig 1 are listed in Table 1. In this table, the parameters, \( a_i, b_i, a_e, b_e, V_i \) and \( V_e \) for inspiration and expiration of pre- or post-injury pig for each segment are listed.

The basic one-segment model given in equations (4) and (5) has been generalized to a multi-segment model by assuming that the compliance functions \( C_i(V) \) and \( C_e(V) \) vary according to equations (7) and (8), which results in the following multi-segment model.

**Inspiration**

\[
R_i \left( \frac{dV_i}{dt} \right) + \frac{V_i}{a_i + b_i(V_i + V_{ex})} + P_{es} = P_{set},
\]

\[
t_{ins} \leq t \leq t_{i1}, \quad j = 1, 2, \ldots, J,
\]

**Expiration**

\[
R_e \left( \frac{dV_e}{dt} \right) + \frac{V_e}{a_e + b_e(V_e + V_{ex})} + P_{es} = P_{peep},
\]

\[
t_{ins} + t_{e(k-1)} \leq t \leq t_{ins} + t_{ek},
\]

where \( t_{i0} = t_{e0} = t_{i0}, t_{e0} \) and \( t_{ek} = t_{ek} \). The initial and boundary
Fig 1. An example of $P_e-V$ data for pre-injury (a) and post-injury (b) pig approximated by five-segment compliance functions. The dots represent $P_e-V$ data obtained from the experiments, while the solid lines are the approximate $P_e-V$ curves.

Table 1. The parameters $a$, $b$, and $v$ obtained from the least squares fit of experimental data using five-segment compliance functions during inspiration and expiration periods, for pre- and post-injury pig. The units for $a$, $b$, and $v$ are L/cm H$_2$O, L/cm H$_2$O, and liter (L), respectively.

<table>
<thead>
<tr>
<th>Segment</th>
<th>Parameters</th>
<th>Pre-injury</th>
<th>Post-injury</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Inspiration</td>
<td>Expiration</td>
</tr>
<tr>
<td>1</td>
<td>$a$</td>
<td>0.027363</td>
<td>0.237805</td>
</tr>
<tr>
<td></td>
<td>$b$</td>
<td>0.012846</td>
<td>-0.435540</td>
</tr>
<tr>
<td></td>
<td>$v$</td>
<td>0.30</td>
<td>1.15</td>
</tr>
<tr>
<td>2</td>
<td>$a$</td>
<td>0.027451</td>
<td>0.182155</td>
</tr>
<tr>
<td></td>
<td>$b$</td>
<td>0.016631</td>
<td>-0.268782</td>
</tr>
<tr>
<td></td>
<td>$v$</td>
<td>0.55</td>
<td>0.95</td>
</tr>
<tr>
<td>3</td>
<td>$a$</td>
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<td>0.065133</td>
</tr>
<tr>
<td></td>
<td>$b$</td>
<td>-0.005182</td>
<td>-0.010138</td>
</tr>
<tr>
<td></td>
<td>$v$</td>
<td>0.80</td>
<td>0.60</td>
</tr>
<tr>
<td>4</td>
<td>$a$</td>
<td>0.042238</td>
<td>0.083840</td>
</tr>
<tr>
<td></td>
<td>$b$</td>
<td>-0.008795</td>
<td>-0.029532</td>
</tr>
<tr>
<td></td>
<td>$v$</td>
<td>0.90</td>
<td>0.40</td>
</tr>
<tr>
<td>5</td>
<td>$a$</td>
<td>0.037296</td>
<td>0.147569</td>
</tr>
<tr>
<td></td>
<td>$b$</td>
<td>-0.002475</td>
<td>-0.082240</td>
</tr>
</tbody>
</table>
conditions for the model equations (9) and (10) are \( V_{i_1} = 0, V_{i_2}(t_{i_2}) = V_i, \) and \( V_{k_1}(t_{k_1}) = 0, \) while the solutions are required to satisfy the continuity conditions
\[
V_{i_j}(t_{i_j}) = V_{i_{j+1}}(t_{i_{j+1}}), \quad j = 1, 2, \ldots, J - 1,
\]
and
\[
V_{k_k}(t_{k_k}) = V_{k_{k+1}}(t_{k_{k+1}}), \quad k = 1, 2, \ldots, K - 1.
\]

Applying the above continuity conditions, the following restrictions are to be placed on the parameters of compliance functions:
\[
a_{i(j+1)} = a_i + (b_{ij} - b_{i(j+1)})v_j \quad (11)
\]
and
\[
a_{e(k+1)} = a_e + (b_{ek} - b_{e(k+1)})v_{ch} \quad (12)
\]
The unknown \( P_{ex} \) is determined by the equation
\[
V_{e_k}(t_{e_k}) = 0. \quad \text{The parameters } v_{i_1}, v_{i_2}, \ldots, v_{i(J-1)} \text{ for inspiration, and } v_{e_1}, v_{e_2}, \ldots, v_{e(K-1)} \text{ for expiration, are inputs of the model, and are obtained from the experimental data. The transition times, } t_{ij} \text{ and } t_{ek}, \text{ which appear in the model equations (9) and (10) are found from the equations }
\]
\[
V_{i_j}(t_{i_j}) = v_{i_j} - V_{ex} \quad \text{and } \quad V_{e_k}(t_{e_k}) = v_{e_k} - V_{ex},
\]
where \( j = 1, 2, \ldots, J \) and \( k = 1, 2, \ldots, K \), respectively.

In order to carry out the simulation of the multi-segment model, the numbers \( J \leq 5 \) and \( K \leq 5 \) of the segments for the variable compliance, which depend on the values of \( V_i \) and \( V_e \), are required. Depending on the values of \( V_i \) and \( V_e \), we then classify the segments during the inspiratory and expiratory periods by means of the values of the times \( t_{ij} \) and \( t_{ek} \), and the compartmental volumes \( v_{i_j} \) and \( v_{ek} \), as follows.

The five segments used in the simulation during the inspiratory period are

1st segment: \( 0 \leq t < t_{i_1} \) and \( 0 \leq V(t) \leq V_{i_1} \),
2nd segment: \( t_{i_1} \leq t < t_{i_2} \) and \( V_{i_1} \leq V(t) \leq V_{i_2} \),
3rd segment: \( t_{i_2} \leq t < t_{i_3} \) and \( V_{i_2} \leq V(t) \leq V_{i_3} \),
4th segment: \( t_{i_3} \leq t < t_{i_4} \) and \( V_{i_3} \leq V(t) \leq V_{i_4} \),
and, 5th segment: \( t_{i_4} \leq t \leq t_{i_5} \) and \( V_{i_4} \leq V(t) \leq V_{i_5} \).

Similarly, the five segments used in the simulation during the expiratory period are

1st segment: \( t_{e_1} \leq t < t_{e_2} + t_{e_1} \) and \( 0 \leq V(t) \leq v_{e_1} \),
2nd segment: \( t_{e_2} + t_{e_1} \leq t < t_{e_3} + t_{e_1} \) and \( v_{e_1} \leq V(t) \leq V_{e_2} \),
3rd segment: \( t_{e_3} + t_{e_1} \leq t < t_{e_4} + t_{e_1} \) and \( V_{e_2} \leq V(t) \leq V_{e_3} \),
4th segment: \( t_{e_4} + t_{e_1} \leq t \leq t_{e_5} + t_{e_1} \) and \( V_{e_3} \leq V(t) \leq V_{e_4} \),
and, 5th segment: \( t_{e_5} + t_{e_1} \leq t \leq t_{e_6} + t_{e_1} \) and \( V_{e_4} \leq V(t) \leq V_{e_5} \).

Hence, 225 cases are possible depending on whether \( v_{i_j} \) or \( v_{e_k} \) exceed \( V_{i} \) or \( V_{ex} \), when attempting to obtain the best fit. A Mathematica program was written for the multi-segment model that covers these 225 cases to calculate the lung volume over one breathing cycle for parameter settings obtained above. From the above conditions shown in the expressions (13) and (14), five segments will be applied to both inspiration and expiration in the model simulation if \( 0 < V_{ex} < v_{i_1}, v_{i_4} < V_i, 0 < V_{ex} < v_{e_4} \) and \( v_{e_1} < V_e \). In Fig. 2, the resulting \( P_{ex} - V \) curves subjected to the continuity conditions (11) and (12) are shown for both pre- and post-injury cases of a particular pig. The parameters used in this data fitting are as listed in Table 1. The compliance functions in the simulations of the \( P_{ex} - V \) curves shown in Fig. 2 are presented in Fig 3. In Figs 2 and 3, the dashed lines indicate the volumes at which the compliance function changes its form, while the solid vertical lines in the graphs shown in Figure 3 indicate the values of \( V_i \) and \( V_e + V_{ex} \).

A simulation of the multi-segment variable compliance model can be seen as solid curves in Figure 4, which shows the lung volume over one breathing cycle for pre- and post-injury cases using the parameter values given in Table 1 obtained by curve fitting of the \( P_{ex} - V \) data shown in Fig 1. In this simulation, the compliance functions for inspiration and expiration are different. Here, in the pre-injury case, four segments are used for inspiration period and two segments are used for expiration period since we have and during inspiration, while and during expiration. In the post-injury case, on the other hand, two segments are used for inspiration period and one segment is used for expiration period since we have \( v_{i_1} < V_{ex} < V_{i_2} \) and \( v_{e_4} < V_{ex} < V_{e_5} \) during inspiration, while \( v_{i_4} < V_{ex} < v_{e_3} \) and \( v_{e_3} < V_{e} < v_{e_4} \) during expiration in the post-injury case. Then, the segments numbered 2-5 and numbered 1-2 as shown in equation (13) are used in the simulation during inspiration for pre- and post-injury cases, respectively, while the segments numbered 2-3 and numbered 1 as shown in equation (14) are used in the simulation during expiration for pre- and post-injury cases, respectively. Therefore, for both pre- and post-injury cases, the multi-segment models are of the form given in equations (9) and (10), where \( j = 2, 3, 4, 5 \) and \( k = 2, 3, 4, 5 \) for pre-injury case, while for post-injury case, \( j = 1, 2, 3, 4, 5 \). Here, we assume \( t_{i_1} = 0 \) and \( t_{i_5} = 0 \) as the starting times for the inspiration period in the pre- and post-injury cases, respectively, and \( t_{e_1} = 0 \) as the starting times for the expiration period in both pre- and post-injury cases. Also, \( t_{e_5} = t_{e_6} \) as the ending times for the inspiration and expiration periods for both pre- and post-injury cases.

Having the compartment volume, the key outcome variables of the clinical interest; namely, tidal volume
Fig 2. Continuous $P_e-V$ curve for pre-injury (a) and post-injury (b) pig using five-segment approximating compliance function subject to continuity conditions (11) and (12). The arrow indicates inspiration (↑) or expiration (↓).

Fig 3. Compliance functions used in Fig 3. The dashed lines indicate the volumes at which the compliance function changes its form and the solid lines indicate $V_{ex}$ and $V_T+V_{ex}$.

Fig 4. Comparison of constant compliance and multi-segment variable compliance models. Here, the lung volume curves are simulated over one breath by multi-segment model, in pre-injury case (a) with $P_{set}=35$ cm H2O, $P_{peep}=5$, $t_{ins}=6s$, $t_{exp}=2s$, $R=16$ cm H2O/L/s and $R=17$ cm H2O/L/s, and in post-injury case (b) with $P_{set}=35$ cm H2O, $P_{peep}=15$, $t_{ins}=6s$, $t_{exp}=3s$, $R=13.75$ cm H2O/L/s and $R=14.25$ cm H2O/L/s. The solid curves correspond to the lung volume obtained from the multi-segment models, and the dashed curves correspond to the volume obtained from the constant compliance models with $C=C^{50}=0.0335536$ and $C=C^{50}=0.0296673$ L/cm H2O for pre- and post-injury cases, respectively. The dots indicate the real data. The solid vertical lines indicate the time $t_{ins}$. 
Fig 5. The end-expiratory pressures, tidal volumes, average volumes, and mean alveolar pressures, for both pre-injury (a) and post-injury (b) cases, obtained from the multi-segment model and the constant compliance model, as functions of breathing frequency. The plus signs (+) indicate quantities obtained from the multi-segment model, and the dots (·) indicate those from the constant compliance model.
In the pre- and post-injury cases, respectively.

In Table 2, the computed values of the clinical outcomes are given for a particular pig in pre- and post-injury cases using the model equations (9) and (10). In this table, we can see that the tidal volume and average volume decrease with the increasing level of PEEP for both pre- and post-injury cases. At each level of PEEP, the reductions in the tidal and average volumes are approximately 3% in the pre-injury case and approximately 5% in the post-injury case, while the increases in the mean alveolar pressures are more moderate. However, approximately 82% and 70% of the beginning (PEEP = 0) tidal and average volumes still remain at the last level of PEEP (PEEP = 6) in pre- and post-injury cases, respectively.

**Comparison of Models**

The changes in the clinical outcomes variables as functions of the breathing frequency \( f \) and duty cycle \( D \) are now investigated. This could yield the optimal choice of and for a clinical setting of \( P_{c, \text{set}} \) and \( P_{c, \text{peep}} \). Using the multi-segment variable compliance model and the constant compliance model, numerical simulations for some clinical important outcomes will be carried out as functions of \( f \). Then, the comparisons of these models are made.

We first consider a linear model for pressure controlled ventilation with constant compliance \( C \). This model is given by the differential equations (2) and (3) when \( e_1 = e_2 = 1 \) and \( C(V_i + V_{ex}) = C(V_i + V_{ex}) = C \).

Here, we use the average inspiratory compliance \( c_{i, \text{ave}} \) from the multi-segment model to approximate the value of \( C \). Thus, the average compliance during inspiration was calculated by means of the formula

\[
c_{i, \text{ave}} = \frac{1}{V_f} \sum_{j=1}^{N} \left( \int_{t_{j-1}}^{t_j} \frac{V_i(t)}{C_i(V_i(t) + V_{ex})} \, dt \right) + \frac{1-D}{t_{tot} - t_{ins}} \sum_{j=1}^{N} \left( \int_{t_{j-1}}^{t_j} \frac{V_i(t)}{C_i(V_i(t) + V_{ex})} \, dt \right)
\]

where \( D \) denotes the inspiratory time fraction, \( t_{ins}/t_{tot} \), or the duty cycle. The intervals, \([t_{j-1}, t_j]\) and \([t_{ins}, t_{tot}]\), are the subintervals of \([0, t_{tot}]\) and \([t_{ins}, t_{tot}]\), respectively, for the different segments in the variable compliance model.

In Table 2, the computed values of the clinical outcomes are given for a particular pig in pre- and post-injury cases using the model equations (9) and (10). In this table, we can see that the tidal volume and average volume decrease with the increasing level of PEEP for both pre- and post-injury cases. At each level of PEEP, the reductions in the tidal and average volumes are approximately 3% in the pre-injury case and approximately 5% in the post-injury case, while the increases in the mean alveolar pressures are more moderate. However, approximately 82% and 70% of the beginning (PEEP = 0) tidal and average volumes still remain at the last level of PEEP (PEEP = 6) in pre- and post-injury cases, respectively.

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We first consider a linear model for pressure controlled ventilation with constant compliance \( C \). This model is given by the differential equations (2) and (3) when \( e_1 = e_2 = 1 \) and \( C(V_i + V_{ex}) = C(V_i + V_{ex}) = C \).

Here, we use the average inspiratory compliance \( c_{i, \text{ave}} \) from the multi-segment model to approximate the value of \( C \). Thus, the average compliance during inspiration was calculated by means of the formula

\[
c_{i, \text{ave}} = \frac{1}{V_f} \sum_{j=1}^{N} \left( \int_{t_{j-1}}^{t_j} \frac{V_i(t)}{C_i(V_i(t) + V_{ex})} \, dt \right) + \frac{1-D}{t_{tot} - t_{ins}} \sum_{j=1}^{N} \left( \int_{t_{j-1}}^{t_j} \frac{V_i(t)}{C_i(V_i(t) + V_{ex})} \, dt \right)
\]

where \( D \) denotes the inspiratory time fraction, \( t_{ins}/t_{tot} \), or the duty cycle. The intervals, \([t_{j-1}, t_j]\) and \([t_{ins}, t_{tot}]\), are the subintervals of \([0, t_{tot}]\) and \([t_{ins}, t_{tot}]\), respectively, for the different segments in the variable compliance model.

In Table 2, the computed values of the clinical outcomes are given for a particular pig in pre- and post-injury cases using the model equations (9) and (10). In this table, we can see that the tidal volume and average volume decrease with the increasing level of PEEP for both pre- and post-injury cases. At each level of PEEP, the reductions in the tidal and average volumes are approximately 3% in the pre-injury case and approximately 5% in the post-injury case, while the increases in the mean alveolar pressures are more moderate. However, approximately 82% and 70% of the beginning (PEEP = 0) tidal and average volumes still remain at the last level of PEEP (PEEP = 6) in pre- and post-injury cases, respectively.

**Comparison of Models**

The changes in the clinical outcomes variables as functions of the breathing frequency \( f \) and duty cycle \( D \) are now investigated. This could yield the optimal choice of and for a clinical setting of \( P_{c, \text{set}} \) and \( P_{c, \text{peep}} \). Using the multi-segment variable compliance model and the constant compliance model, numerical simulations for some clinical important outcomes will be carried out as functions of \( f \). Then, the comparisons of these models are made.

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ventilation $V_\ell = fV_T$, the mean alveolar pressure $P_\ell$, and the power (work per minute) $W_m = fW_{br}$, where $W_m$ is the work per breath and is given by $P_\ell V_T$. We will investigate these quantities as the breathing frequency $f$ tends to infinity, treating first the one-segment model in which the compliances are linear functions of $V$.

We define the frequency $f$ cycle/min, and the duty cycle $D = t_i / t_{tot}$, so that $t_i = 60DF/f$ seconds and $t_i = 60(D-1)/f$ seconds. Letting $\Delta P = P_{set} - P_e$ and $\Delta P_e = P_{ex} - P_e$, equations (4) and (5) then become

$$R_e \left( \frac{dV_e}{dt} \right) + \frac{V_e}{a_e + b_e(V_e + V_{cx})} = \Delta P_e, \, 0 \leq t \leq t_{in} \quad (18)$$

$$R_e \left( \frac{dV_e}{dt} \right) + \frac{V_e}{a_e + b_e(V_e + V_{cx})} = \Delta P_e, \, t_{in} < t \leq t_{tot} \quad (19)$$

These can be solved in a straightforward fashion to yield

$$e^{\alpha_i t} \left( \frac{A_i + B_i V_e}{A_i} \right) \frac{V_e}{B_i} = e^{\frac{t_{in}}{B_i}}, \, 0 \leq t \leq t_{in} \quad (20)$$

and

$$e^{\alpha_i (V_e - V_i)} \left( \frac{A_i + B_i V_e}{A_i + B_i V_T} \right) \frac{V_e}{B_i} = e^{\frac{t_{in}}{B_i}}, \, t_{in} < t \leq t_{tot} \quad (21)$$

where

$$A_i = (a_i + b_i V_{cx}) \Delta P_i, \quad A_e = (a_e + b_e V_{cx}) \Delta P_e \quad (22)$$

$$B_i = b_i \Delta P_i - 1, \quad B_e = b_e \Delta P_e - 1 \quad (23)$$

$$\alpha_i = \frac{b_i}{B_i}, \quad \alpha_e = \frac{b_e}{B_e} \quad (24)$$

and

$$\beta_i = \frac{a_i + b_i V_{cx}}{B_i}, \quad \beta_e = \frac{a_e + b_e V_{cx}}{B_e}. \quad (25)$$

### Tidal Volume

We recall that $V_i(t_i) = V_\ell$, so that (20) yields

$$e^{\alpha_i t_i} \left( \frac{A_i + B_i V_\ell}{A_i} \right) \frac{V_\ell}{B_i} = e^{\frac{t_i}{B_i}}. \quad (26)$$

We now note that all terms in equation (18) are positive and therefore,

$$P_e < \lim_{t_i \to \infty} P_e \quad (27)$$

where the superscript $\infty$ denotes the limiting value of each of the above quantities. Notice that the graph of the left hand side of (27) is a straight line through the origin ($V_T^\infty$ being the independent variable) and the graph of the right hand side is that of a logarithmic function of $V_T^\infty$, also passing through the origin. The values of that satisfy (27) are the intersection of the line with the logarithmic curve. Using (22)-(25), we can show that

$$\alpha_i > \frac{\beta_i}{A_i}$$

and therefore the slope at the origin of the straight line is greater than that of the logarithmic curve. Hence, the two curves intersect only at the origin, which means that

$$V_T^\infty = \lim_{f \to \infty} V_T = 0. \quad (28)$$

We note that this is the same result as in the constant compliance case proposed by Marini & Crooke in 1993.$^{29}$

### End-expiratory Pressure

We recall that $V_i(t_i) = 0$, so that (21) yields

$$-\alpha_i \left( \frac{A_i}{A_i + B_i V_T} \right) \frac{V_T}{B_i} = e^{\frac{t_i}{B_i}}. \quad (29)$$

From (29), we obtain

$$t_e = R_e \left[ \frac{\beta_i}{B_i} \ln \left( 1 + \frac{B_i}{A_i} V_T \right) - \alpha_i V_T \right]. \quad (30)$$

As $f$ increases, $t_e$ decreases, so that differentiation of both sides of (30) with respect to $t_e$ results in the following equation.

$$1 = R_e \left[ \frac{\beta_i}{B_i} \ln \left( 1 + \frac{B_i}{A_i} V_T \right) - \alpha_i V_T' \right]$$

where the prime denotes the derivative with respect to $t_e$. We now let $f \to \infty$, recalling that $V_T \to 0$, and obtain

$$V_T' \to -\frac{A_i}{(a_i + b_i V_{cx}) R_e}. \quad (31)$$

Since $t_e = 60(1-D)/f$, one arrives at
\[ \frac{dV_t}{df} \rightarrow 60(1-D)A_v^\alpha \text{ as } f \rightarrow \infty. \quad (31) \]

On the other hand, the same can be done with the equation (20) to arrive at
\[ \frac{dV_t}{df} \rightarrow -60DA_v^\alpha \text{ as } f \rightarrow \infty. \quad (32) \]

Equating (31) and (32), one then obtains
\[ (1-D)A_v^\alpha = -DA_v^\alpha \]
\[ \frac{(a_v + b_v V_{ex}) R_e}{(a_v + b_v V_{ex}) R_i}. \]

Using (22), and the corresponding definitions of \( \Delta P_\omega \), \( \omega = i, e \), we then find that
\[ \ln y = k f \ln \left( \frac{A_v}{A_v + f B_v V_T} \right). \]

which tends to an indeterminate form \( \infty \cdot 0 \) as \( f \rightarrow \infty \), thus allowing for the use of L’Hôpital’s rule. This yields
\[ \lim_{f \rightarrow \infty} \ln y = -60(1-D) \frac{b_v R_e}{b_v R_i}. \quad (35) \]

Using (35) while letting \( f \rightarrow \infty \) in (34) yields
\[ \lim_{f \rightarrow \infty} V_T = -60(1-D) \left( \frac{B_v^\alpha}{b_v R_e} + 1 \right) \]
\[ \text{or} \]
\[ \dot{V}_T^\infty = \frac{60D(1-D)(P_{set} - P_{peep})}{DR_e + (1-D)R_i}. \quad (36) \]

\textbf{Mean Alveolar Pressure}

The mean alveolar pressure is defined as
\[ P_m = D \int_{t_{in}}^{t_{ex}} \frac{V_t - P_{peep}}{C_e(V_v + V_{ex})} dt \]
\[ + \frac{1-D}{t_{ex}} \int_{t_{in}}^{t_{ex}} \frac{V_t}{C_e(V_v + V_{ex})} dt + P_{ex}. \quad (37) \]

On using equations (18) and (19) to substitute for
\[ C_e(V_v + V_{ex}) \] and \[ C_e(V_v + V_{ex}) \]
respectively, it is then straightforward to carry out the integrations. As a result, we obtain the following expression for the mean alveolar pressure as a function of \( f \):
\[ P_m = D \Delta P_i + (1-D) \Delta P_e + \frac{(R_e - R_i) f V_T}{60} + P_{ex}. \]

Thus, we let \( f \rightarrow \infty \) and use (33) and (36) to obtain the limiting value \( P_m^\infty \) of \( P_m \) as:
\[ P_m^\infty = \frac{DR_{P_{set}} + (1-D)R_u P_{peep}}{DR_e + (1-D)R_i}. \quad (38) \]

We note that \( P_m^\infty = P_{ex}^\infty \) which is the same as that which has been discovered in the constant compliance case.\(^6\)

\textbf{Power}

The power, \( W_{br} \), is defined as the frequency times the work per breath, which has been shown to be equal to \( P_{set} V_T \). Therefore
\[ W_{m} = f P_{set} V_T \]
and hence
\[ \dot{W}_{m} = \dot{P}_{set} V_t = \dot{P}_{set} \dot{V}_T. \]

Using (36), one then finds
\[ \dot{W}_{m}^\infty = \frac{60D(1-D)(P_{set} - P_{peep}) P_{set}}{DR_e + (1-D)R_i}. \quad (39) \]

The limits evaluated in this paper are summarized in Table 3. When compared with the limits obtained for the constant compliance models with linear resistive pressure \( P_r = RQ \), studied by Marini et al. in 1989,\(^30\) and nonlinear resistive pressure \( P_r = RQ^\epsilon \) presented by Crooke & Marini in 1993,\(^6\) we notice that there are slight differences. In the previous works, it was assumed that \( P_{peep} = 0 \) and hence, the formulae given in Table 3 are more general. Also, the calculation of the limiting value \( P_{ex}^\infty \) is new. Otherwise, the limiting values in the case of linear resistive pressure, with constant and variable compliances, are the same.

Furthermore, we note that the limiting values of the key outcome variables obtained from the one-segment model agree with the corresponding values derived for
Table 2. Tidal volumes, end-expiratory pressures, mean alveolar pressures, and average lung volumes for different levels of applied PEEP using the multi-segment model for both pre- and post-injury cases with $P_{set} = 35 \text{ cm H}_2\text{O}$ and $t_m = 6s$. Here, in the pre-injury case, $R_i = 18 \text{ cm H}_2\text{O}/L/s$, $R_e = 15 \text{ cm H}_2\text{O}/L/s$ and $D = 1/3$, and in the post-injury case, $R_i = 13.75 \text{ cm H}_2\text{O}/L/s$, $R_e = 14.25 \text{ cm H}_2\text{O}/L/s$ and $D = 1/2$.

<table>
<thead>
<tr>
<th>PEEP</th>
<th>$V_t$ (Liters)</th>
<th>$P_{ex}$ (cm H$_2$O)</th>
<th>$P_m$ (cm H$_2$O)</th>
<th>$V_{ave}$ (Liters)</th>
<th>$V_t$ (Liters)</th>
<th>$P_{ex}$ (cm H$_2$O)</th>
<th>$P_m$ (cm H$_2$O)</th>
<th>$V_{ave}$ (Liters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>1.09810</td>
<td>1.02785</td>
<td>16.7525</td>
<td>0.59194</td>
<td>1.04794</td>
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<td>0.73416</td>
</tr>
<tr>
<td>1.0</td>
<td>1.06547</td>
<td>1.91729</td>
<td>17.1220</td>
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<td>0.69830</td>
</tr>
<tr>
<td>2.0</td>
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<td>2.80452</td>
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<td>0.92513</td>
<td>2.11974</td>
<td>16.3799</td>
<td>0.66341</td>
</tr>
<tr>
<td>3.0</td>
<td>1.00180</td>
<td>3.68633</td>
<td>17.9185</td>
<td>0.53436</td>
<td>0.86750</td>
<td>3.11500</td>
<td>17.0120</td>
<td>0.62950</td>
</tr>
<tr>
<td>4.0</td>
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<td>4.60791</td>
<td>18.3972</td>
<td>0.51764</td>
<td>0.81240</td>
<td>4.11019</td>
<td>17.6383</td>
<td>0.59659</td>
</tr>
<tr>
<td>5.0</td>
<td>0.94011</td>
<td>5.57522</td>
<td>18.9963</td>
<td>0.50359</td>
<td>0.75982</td>
<td>5.10533</td>
<td>18.2587</td>
<td>0.56468</td>
</tr>
<tr>
<td>6.0</td>
<td>0.90943</td>
<td>6.54479</td>
<td>19.5109</td>
<td>0.48709</td>
<td>0.70974</td>
<td>6.10045</td>
<td>18.8735</td>
<td>0.53377</td>
</tr>
</tbody>
</table>

Table 3. Limiting values for variable compliance model.

<table>
<thead>
<tr>
<th>Outcome Variables</th>
<th>Formulae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidal Volume</td>
<td>$V_T^\infty = 0$</td>
</tr>
<tr>
<td>End-expiratory Pressure</td>
<td>$P_{ex}^\infty = \frac{D R_e P_{set} + (1 - D) R_i P_{peep}}{D R_e + (1 - D) R_i}$</td>
</tr>
<tr>
<td>Minute Ventilation</td>
<td>$\dot{V}<em>E^\infty = \frac{60 D (1 - D) (P</em>{set} - P_{peep})}{D R_e + (1 - D) R_i}$</td>
</tr>
<tr>
<td>Mean Alveolar Pressure</td>
<td>$P_m^\infty = P_{ex}^\infty$</td>
</tr>
<tr>
<td>Power</td>
<td>$\dot{W}<em>m^\infty = \frac{60 D (1 - D) (P</em>{set} - P_{peep}) P_{set}}{D R_e + (1 - D) R_i}$</td>
</tr>
</tbody>
</table>
the constant compliance model.\textsuperscript{5,30} This is to be expected since it was found that these limiting values are independent of the compliances of the system and only depend on the duty cycle $D$, the respiratory resistance constants $R_i$ and $R_e$, and the applied pressures $P_{set}$ and $P_{peep}$. This leads us to conclude that the same will be found for the multi-segment model. In fact, the outcome variables plotted in Fig 5 do indeed tend to their respective limiting values given by the formulae in Table 3 as $f \rightarrow \infty$.

**Discussion and Conclusion**

It has been recently discovered experimentally and clinically that high pressure mechanical ventilation at volumes above the upper inflection point can cause lung damage. The current ventilatory strategies are aimed at avoiding overdistention and repetitive cycles of recruitment-derecruitment. In such cases, pressure targeted ventilation with high applied PEEP provides a valuable adjunct, since it restricts the maximal alveolar pressure. Hence, these strategies with high applied PEEP may minimize lung injury. Furthermore, pressure limiting ventilatory strategies have been shown to lower mortality in ARDS.

A mathematical model for pressure controlled ventilation with multi-segment variable compliance function has been developed and presented in this paper. The clinical important outcomes can then be computed using this multi-segment model. In Table 2, the tidal volume $V_t$, end-expiratory pressure $P_{e}$, mean alveolar pressure $P_{alve}$, and average lung volume $V_{ave}$, are given for different levels of applied PEEP. These calculations illustrate the usefulness of a mathematical model, being a means by which we can experiment with the ventilatory parameters to achieve the desired levels of the clinical outcome variables. Here, we observe that the tidal and average volumes decrease with increasing levels of applied PEEP.

Moreover, the tidal volume diminishes significantly with increasing breathing frequency in the simulation obtained from the constant model. The decline arises from the effects of shortened inspiratory time. The multi-segment model predicts a much smaller decrease than the effects of shortened inspiratory time. The multi-segment model predicts a much smaller decrease than that predicted by the constant compliance model.

Although some other researchers on this topic have attempted to fit the $P_{alve}V$ curve with continuous functions, such as the sigmoidal function used by Venegas et al.,\textsuperscript{14} the resulting models become quite intractable mathematically which is less desirable for analytical proposes. The multi-segment model given in equations (9) and (10) for pressure controlled ventilation has been found to be mathematically tractable and give accurate simulations of mechanical ventilation of normal and injured lungs. The model may be used to study effects of clinical-set inputs on the key ventilatory outcome variables in pigs. The ability to predict these effects can be extremely useful in optimizing ventilatory strategies in the clinical setting for humans.

**Acknowledgments**

The authors would like to thank the Thailand Research Fund and the National Research Council of Thailand for the financial support.

**References**

5. Burke WC, Crooke PS, Marcy TW, Adams AB and Marini JJ (1996) A general two-compartment model for mechanical ventilation of normal and injured lungs. The model may be used to study effects of clinical-set inputs on the key ventilatory outcome variables in pigs. The ability to predict these effects can be extremely useful in optimizing ventilatory strategies in the clinical setting for humans.


