Theoretical Study of Inspiratory Flow Waveforms during Mechanical Ventilation on Pulmonary Blood Flow and Gas Exchange

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A lumped two-compartment mathematical model of respiratory mechanics incorporating gas exchange and pulmonary circulation is utilized to analyze the effects of square, descending and ascending inspiratory flow waveforms during mechanical ventilation. The effects on alveolar volume variation, alveolar pressure, airway pressure, gas exchange rate, and expired gas species concentration are evaluated. Advantages in ventilation employing a certain inspiratory flow profile are offset by corresponding reduction in perfusion rates, leading to marginal effects on net gas exchange rates. The descending profile provides better CO₂ exchange, whereas the ascending profile is more advantageous for O₂ exchange. Regional disparities in airway/lung properties create maldistribution of ventilation and a concomitant inequality in regional alveolar gas composition and gas exchange rates. When minute ventilation is maintained constant, for identical time constant disparities, inequalities in compliance yield pronounced effects on net gas exchange rates at low frequencies, whereas the adverse effects of inequalities in resistance are more pronounced at higher frequencies. Reduction in expiratory air flow (via increased airway resistance) reduces the magnitude of upstroke slope of capnogram and oxigram time courses without significantly affecting end-tidal expired gas compositions, whereas alterations in mechanical factors that result in increased gas exchanges rates yield increases in CO₂ and decreases in O₂ end-tidal composition values. The model provides a template for assessing the dynamics of cardiopulmonary interactions during mechanical ventilation by combining concurrent descriptions of ventilation, capillary perfusion, and gas exchange.

Key Words: ventilatory mechanics; pulmonary circulation; convective–diffusive gas transport.

INTRODUCTION

Mechanical ventilation is one of the major supporting therapeutic modalities used to manage critically ill patients with acute or chronic respiratory failure
The implicit goal of mechanical ventilation is to assure or restore appropriate levels of gas exchange at the lungs with minimal alterations of other physiological functions. Because of the interactions between the patient and the ventilator, physiological quantities (e.g., minute ventilation, alveolar gas exchange, pulmonary blood flow, cardiac output, work of breathing) can be significantly affected by the choice of ventilatory mode. Rational application of clinical therapies during ventilator management therefore requires an understanding of the underlying physiological mechanisms at play during mechanical ventilation, particularly when different ventilatory patterns are employed.

Experimental studies examining the effects of mechanical ventilatory mode on gas exchange and pulmonary hemodynamics have been reported. Numerous studies using mechanical lung models, animal models, and human studies have concurred in their assessment that the descending waveform yields improved distribution of ventilation. Opinion is divided, however, over the relative effectiveness of individual waveforms on gas exchange. Reports varied from gas exchange being insignificantly affected to that favoring the descending waveform while the ascending waveform was picked to perform better elsewhere. Comparison was difficult in the clinical studies, since changing the inspiratory waveform also induced changes in tidal volume and duty cycle. A theoretical study predicted that changes in both inspiratory and expiratory flow patterns can result in different steady state blood gas tensions and gas exchange. Significant differences in carbon dioxide elimination, as measured by end-tidal carbon dioxide partial pressure, were reported with inspiratory waveforms; higher end-tidal values were obtained with the ascending waveform than with the square and descending waveforms. A relatively recent survey of the literature has concluded that no definitive statement could be made regarding the superiority of either flow pattern over the other. The only consistent result across all studies was that cardiovascular performance was not affected differently by either flow pattern. The inability to make concrete inferences resulted from: (i) inconsistent ventilator settings across the experiment set (such as low tidal volumes, short duty cycles and use of postinspiratory pause, insignificant changes in peak flow); (ii) presence of morphological differences in the flow patterns used; (iii) design employed, such as the absence of randomized trials or repeated-measures; (v) small size of sample population studied; and (vi) failure to segregate samples by disease process. In that report, major factors attributed to the inability to maintain standardized settings were the number of dynamic and confounding variables encountered (e.g., changes in pulmonary perfusion, sedation effects, inotropes, and diuretics) and unstable patient states that could in themselves have accounted for inconsistencies in the conclusions reported.

This paper provides a template for quantitatively characterizing the dynamic effects of intermittent positive pressure mechanical ventilation on capillary perfusion and ensuing gas exchange. A lumped two-compartment mathematical model of respiratory mechanics incorporating descriptions of gas exchange and pulmonary blood flow is employed for this purpose. The generalized framework facilitates the investigation of problems pertaining to the interaction of mechanical ventilation
on cardiovascular dynamics and gas exchange. An idealized flow generator (time-
cycled) with prespecified tidal volume and duty cycle is applied to generate a
given flow pattern. The categories of flow patterns assessed (square, ascending,
and descending) are those available in modern microprocessor controlled ventilators
(4). The objectives of this study were to: (a) assess the effects of choice of inspiratory
flow waveforms on gas exchange as well as on alveolar volume variation, alveolar
pressure, airway pressure, expired gas species concentration (e.g., oxigram and
capnogram), and regional pulmonary blood flow for a given minute ventilation
rate; (b) evaluate quantitative indices such as the ventilation, regional blood-gas
concentrations, and pulmonary blood flow distribution ratios; and (c) investigate
the effect of cycling frequency on regional ventilation, perfusion, and gas exchange.

METHODS

Model Development

1. Patient-ventilator model. The respiratory system was considered as a lumped
system composed of a rigid anatomic dead space region in series with two parallel
compliant alveolar compartments (Fig. 1). Time-varying volume changes produced
by deformation of the elastic alveolar compartments were characterized using linear
pressure–volume relationships with compliances denoted by $C_{A1}$ and $C_{A2}$, respec-
tively. Viscous dissipation caused by motion of the elastic alveolar structure (42,
43) was ignored, however. Air flow through the peripheral conduits of the bronchial
tree feeding the individual alveolar compartments was characterized by lumped
airway resistances ($R_1$ and $R_2$, respectively). The alveolar compartments communi-
cated only through the branch point. Nonlinear flow-dependent resistance to airflow
offered by the upper airways (40) was ignored. The subject was assumed to be
intubated; hence the resistance to airflow offered by an endotracheal tube was
modeled by a fixed airway resistance ($R_{UAW}$). All driving frequency changes
considered herein do not exceed 1 Hz. Hence the inertial effects of gas acceleration
were ignored in the present formulation.

Air forced into the lungs during positive pressure ventilation performs work on
the lung and chest wall, as well as on the air already present in the system (17).
This is characterized by including the compressibility of air ($C_{g1}$, $C_{g2}$, and $C_{gu}$ in
Fig. 1; derived using the ideal gas law) at each nodal pressure site. A subject
undergoing mechanical ventilation was assumed to be sedated; hence the diaphragm
and chest wall were assumed to behave passively and their motion was described
using a passive lumped compliant element ($C_{th}$). Changes in pressure across the
lumped thoracic cavity (viz., intrapleural pressure, $P_{PL}$) were then characterized
by a constant value for this compliance (23, 35). Viscous resistance to flow was
also neglected in considering chest wall dynamics; it is generally considered to be
small both in health and in disease (16, 19, 23).

2. Pulmonary circulation model. A lumped system composed of compliant
pulmonary arterial, capillary, and venous regions (denoted by $C_a$, $C_{c1}$, $C_{c2}$, and $C_v$,
respectively) was employed. Resistance to blood flow offered in each of the regions
(denoted by $R_a$, $R_{c1}$, $R_{c2}$, and $R_v$, respectively) subsequently dictated regional
Constant pressure sources of 15 and 5 mm Hg with respect to $P_{PL}$ were used to denote the mean pulmonary arterial ($P_{pa}$) and venous ($P_{pv}$) pressures, respectively. This implied that instantaneous changes in $P_{pa}$ and $P_{pv}$ due to the pumping action of the right ventricle and the left atrium (auricle) were neglected. The resulting variation in mean blood volume in each of the capillary regions was presumed to be governed by the modulation of the transmural pressure in each region. In the extraalveolar pulmonary arterial and venous regions, the
perivascular pressure was assumed to be the intrapleural pressure; hence volume changes in these regions were dictated by the variation in $P_{PL}$. On the other hand, volume variation in the intraalveolar regional capillary compartments was governed by the changes in the regional alveolar pressure. Blood flow through each alveolar region was then dictated by the pressure drop exhibited across the regional nodes; this regional blood flow rate was combined to yield the total mean blood flow (cardiac output) through the pulmonary circulation.

3. Gas-exchange model. Oxygen, carbon dioxide, and nitrogen were assumed to be transported across the lumped alveolar–capillary barrier solely via diffusion.
Oxygen was taken up by the blood and carbon dioxide was excreted while nitrogen (a relatively inert gas) diffused in either direction dependent on the instantaneous regional overall ventilation–perfusion ratio (49). All compartments were assumed to be well-mixed with the movement of gases in the respiratory system and blood in the pulmonary circulation being primarily through bulk axial convection (considered one-dimensional ignoring all radial variations). Blood was considered as a uniform, single-phase medium with instantaneous chemical reactions; hence species contents were related to the equilibrium tensions using empirical dissociation curves (15, 28, 32, 41) (refer to Appendix C for details). Mixed venous inlet blood gas tensions were held constant throughout the simulations and physiological shunting of blood was ignored.

Employing the model described above (dynamic equations for which are furnished in Appendix A), the objective of this study was to evaluate the effects of different input driving airflow waveforms and frequency changes on respiratory mechanics, pulmonary circulation, and gas exchange for a given set of model parameters. Parameter values describing the compliant and resistive elements in the airway/lung mechanics and pulmonary circulation models for nominal operating conditions (fully recovered patient with endotrachael tube) are listed in Table 1.

On the air side, the model structure was modified and parameter values were adopted from descriptions published elsewhere (22, 23). Heterogeneous lungs were emulated using parallel alveolar regions connecting through a branch point to a common resistive airway. Nominal compliance values for the individual alveolar and thoracic regions in Table 1 were chosen to yield a net compliance of 0.1 L/cm H₂O, a value reported for normal subjects (35). Thoracic compliance value of 0.1 L/cm H₂O was adopted from (23). Nominal peripheral airway resistance values were adopted from (22). Inspiratory and expiratory resistances were chosen to be unequal, consistent with reported observations (7, 13). Upper airway resistance was chosen to be 10 cm H₂O/L/s, an average value for resistance offered to flow by a size 7 endotrachael tube for flow rates between 0.5 and 2 L/s under constant flow conditions (50). On the blood side, the model structure adopted was a modified form of that presented in (12). Parameter values for the pulmonary circulation were chosen to yield nominal values of total cardiac output, total pulmonary volume, and pulmonary arterial and venous volumes. A total pulmonary blood volume of approximately 440 ml was assumed as indicated in (33) for man. The distribution of volumes obtained was different from that reported in (33), however, but was comparable to data reported in (51).

Inspiratory flow waveforms employed in this study were the ascending, descending, and square waveforms. No postinspiratory pause (protoexpiratory pause) was set and the expiratory phase was considered to be purely passive. The total volume of gas introduced per breath at the mouth, cycling frequency (and hence minute ventilation), and duty cycle were unchanged during the comparative study of the four modes of ventilation (at 600 ml/breath, 10 breaths/min, and 0.333, respectively). While investigating the effects of frequency changes the minute ventilation and duty cycle were maintained invariant.
### TABLE 1
Nominal Model Parameters Describing Respiratory Mechanics and Pulmonary Circulation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Value</th>
<th>Units</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endotrachael tube resistance</td>
<td>$R_{UAW}$</td>
<td>10.0</td>
<td>cm H$_2$O</td>
<td>50</td>
</tr>
<tr>
<td>Peripheral airway resistance$^a$</td>
<td>$R_j$</td>
<td>2.0,3.0$^b$</td>
<td>cm H$_2$O/L/s</td>
<td>22</td>
</tr>
<tr>
<td>Pulmonary compliance$^a$</td>
<td>$C_{A_j}$</td>
<td>0.1</td>
<td>L/cm H$_2$O</td>
<td>11</td>
</tr>
<tr>
<td>Chest wall compliance</td>
<td>$C_{th}$</td>
<td>0.2</td>
<td>L/cm H$_2$O</td>
<td>11</td>
</tr>
<tr>
<td>Inspired O$_2$ mole fraction</td>
<td>$F_{AIO_2}$</td>
<td>0.2089</td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>Inspired CO$_2$ mole fraction</td>
<td>$F_{AICO_2}$</td>
<td>0.0004</td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>Inspired N$_2$ mole fraction</td>
<td>$F_{AIN_2}$</td>
<td>$1 - F_{AIO_2} - F_{AICO_2}$</td>
<td>L/mm Hg</td>
<td>33</td>
</tr>
<tr>
<td>Pulmonary arterial compliance</td>
<td>$C_a$</td>
<td>$4 \times 10^{-3}$</td>
<td>mm Hg/L</td>
<td>33</td>
</tr>
<tr>
<td>Pulmonary capillary compliance</td>
<td>$C_c$</td>
<td>$4.167 \times 10^{-4}$</td>
<td>mm Hg/L</td>
<td>33</td>
</tr>
<tr>
<td>Pulmonary arterial resistance</td>
<td>$R_a$</td>
<td>$0.035 \left( \frac{0.150}{V_c} \right)^2$</td>
<td>mm Hg/L/s</td>
<td>This study</td>
</tr>
<tr>
<td>Pulmonary capillary resistance</td>
<td>$R_c$</td>
<td>$0.042 \left( \frac{0.0375}{V_c} \right)^2$</td>
<td>mm Hg/L/s</td>
<td>This study</td>
</tr>
<tr>
<td>Pulmonary venous resistance</td>
<td>$R_v$</td>
<td>$0.035 \left( \frac{0.200}{V_c} \right)^2$</td>
<td>mm Hg/L/s</td>
<td>This study</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure</td>
<td>$P_{PA}$</td>
<td>15</td>
<td>mm Hg</td>
<td>30</td>
</tr>
<tr>
<td>Mean pulmonary venous pressure</td>
<td>$P_{PV}$</td>
<td>5</td>
<td>mm Hg</td>
<td>30</td>
</tr>
<tr>
<td>Mixed venous O$_2$ tension</td>
<td>$p_{bO_2}$</td>
<td>40.0</td>
<td>mm Hg</td>
<td>49</td>
</tr>
<tr>
<td>Mixed venous CO$_2$ tension</td>
<td>$p_{bCO_2}$</td>
<td>46.0</td>
<td>mm Hg</td>
<td>49</td>
</tr>
<tr>
<td>Mixed venous N$_2$ tension</td>
<td>$p_{bN_2}$</td>
<td>575.0</td>
<td>mm Hg</td>
<td>49</td>
</tr>
<tr>
<td>2–3 DPG Shift factor</td>
<td>DP50</td>
<td>0</td>
<td></td>
<td>This study</td>
</tr>
<tr>
<td>Hemoglobin concentration</td>
<td>Hb</td>
<td>14.4604</td>
<td>g/ml/100 ml</td>
<td>This study</td>
</tr>
</tbody>
</table>

$^a j = 1, 2$ and denotes the individual alveolar regions. $j = 1$ denotes the control alveolus and $j = 2$ designates the affected alveolus throughout this paper.

$^b R_j$ takes on different values during inspiration and expiration (22) with the larger value during expiration.

### Computational Aspects

The resulting ordinary differential equation system was implemented in the “C” programming language. Numerical integration was performed using CVODE, an
implementation of the variable coefficient Adam’s method in Nordsieck form, attributed to Brown et al. (8). CVODE was written by S. D. Cohen and A. C. Hindmarsh at the Lawrence Livermore National Laboratory. A maximum stepsize of $5 \times 10^{-3}$ s and a relative error tolerance of $1 \times 10^{-5}$ were employed. A steady state was achieved after 30 breaths and subsequently used.

RESULTS

Time Courses during Symmetric Regional Ventilation

Computed variables describing respiratory mechanics and pulmonary circulation are depicted in Fig. 3 for the case where the resistive and compliant properties in the individual alveolar regions are set equal (i.e., $R_1 = R_2$ and $C_{A1} = C_{A2}$). Parameter values are as listed in Table 1. Time course of all variables during the inspiratory phase of the ventilation cycle varies significantly for all ventilatory modes; traces for the square pattern (solid lines) lie between the corresponding traces for ascending (dash-dot line) and descending (dash lines) patterns, in general.

1. Airway/lung mechanics. When the resistive and compliant characteristics representing the individual alveolar regions are identical, ventilation at the mouth is equally distributed between the alveolar regions leading to a symmetric expansion in alveolar volume and corresponding buildup of alveolar pressure in the individual regions (Fig. 3). The volume and pressure waveforms depend on the specific alveolar ventilation profile. Higher mean airway pressure is predicted with the descending flow profile. At equivalent tidal volumes and duty cycle, the descending waveform yields the highest cycle-averaged branch-point, intrapleural, and alveolar pressure. In contrast, the ascending waveform provides the lowest values. Peak inflation pressures are highest with the ascending waveform and lowest with the descending waveform. The square profile yields intermediate values. These models predicted that effects on distribution of tidal ventilation and pressure in the airway are similar to those reported previously (5, 22, 23).

A similar comment may be made regarding the qualitative changes in alveolar volume. The descending waveform provides the largest change in initial alveolar volume from the end-expiratory equilibrium value compared to the ascending waveform with the square profile yielding intermediate changes. Since the alveolar compartmental compliances are assumed to be linear, tracings of alveolar pressure changes mirror those of alveolar volume changes. Furthermore, a linear thoracic compliance leads $P_{PL}$ changes to qualitatively mirror alveolar volume changes. Intrapleural pressure rises during the inspiratory phase of IPPV. This is quite unlike spontaneous breathing where $P_{PL}$ is subatmospheric throughout the cycle. Both alveolar and mouth pressures are positive during IPPV, whereas mouth pressure is zero (atmospheric) and alveolar pressure subatmospheric during the inspiratory phase of spontaneous breathing.

2. Pulmonary circulation. During the inspiratory phase, the ensuing rise in $P_{PL}$ and regional $P_A$ tends to decrease the transmural pressure across the compliant elements representing the lumped pulmonary artery-arterioles, regional pulmonary capillaries, and pulmonary venules–vein ($P_{TMa}$, $P_{TMb1,2}$, and $P_{TMv}$, respectively)
FIG. 3. Time course of airway mechanics variables. Regional alveolar resistive and compliant properties are identical. Minute ventilation rate is set at 6 L(BTPS)/min with a cycling frequency of 10 breaths/min and a duty cycle of 0.333. Ascending, descending, and square waveforms are denoted by a, d, and f, respectively in the legend in all the panels.
while simultaneously elevating the pulmonary arterial, regional capillary, and venous nodal pressures, $P_{pa}$, $P_{c1&2}$, and $P_v$, respectively, in Fig. 2. Elevation in $P_{pa}$ reduces the forward pressure gradient, $P_{pa} - P_a$, which then tends to lower total inlet blood flow rate, $Q_a$, on the arterial side. In contrast, the nodal pressure gradient at the outlet, $P_v - P_{pv}$, increases, thereby favoring increased outlet blood flow rate, $Q_v$, on the venous side. The resulting inequality of inlet and outlet blood flow rates points to a reduction in the blood volume stored in the pulmonary circulation at all the compliant elements during the inspiratory phase of mechanical ventilation. Depicted in Fig. 4, this trend is qualitatively consistent with observations made during experimental investigations using a porcine model wherein a reduction in pulmonary blood volume was observed during the inspiratory phase of mechanical ventilation (47, 48).

Blood flow in the arterial, regional capillary, and venous regions ($Q_a$, $Q_{b1&2}^{in}$, $Q_{b1&2}^{out}$, and $Q_v$) are affected by the choice of inspiratory waveform and can be explained by the related effects on intrapleural and alveolar pressures. The descending profile causes the greatest perturbation in the early part of the inspiratory phase, thereby creating significant effects on arterial and venous perfusion rates early on. The early rise in alveolar pressure while employing the descending waveform similarly results in a steeper fall in capillary perfusion rate comparatively because of the concomitant effects on capillary nodal pressure, $P_{c1}$. In contrast, the ascending waveform mainly influences the latter portion of the inspiratory phase and yields the slowest rate of variation. The square profile again grades intermediate. Acting in synchrony, these changes point to a reduction in stored blood volume ($V_a$, $V_{b1&2}$, and $V_v$) during the inspiratory phase.

3. Gas exchange. As indicated in Fig. 5, variables describing gas exchange also show markedly different temporal behavior during the inspiratory phase for the three flow ventilatory modes considered. The greater initial airflow encountered using the descending ventilatory mode (Fig. 3, top row), facilitates better convection in the airway compartments, thereby resulting in higher $O_2$ and lower $CO_2$ cycle-averaged partial pressures in the alveolar and dead space regions. Alveolar composition for the ascending profile initially lags in comparison with the descending and square profiles. This is due to the initial mixing of the dead space air with the alveolar gas combined with gas exchange across the capillary. Gas composition in the expirate corresponds directly with ambient air and is relatively unchanged during the inspiratory phase. Alveolar species partial pressures are presumed to be equal to the end-capillary species blood–gas tensions. No diffusional limitations are considered and the gas exchange across the capillary is assumed to be instantaneous.

During the course of a respiratory cycle, the ensuing variation in the instantaneous $O_2$ and $CO_2$ exchange across the capillary ($\phi_{O_2}$ and $\phi_{CO_2}$, respectively) is proportional to the difference in perfusion rates and the difference in the end-capillary blood species tension (i.e., referenced to a respiratory cycle, $\Delta \phi_{bj} = C_{in_{b1&2}}^{in} - C_{in_{b1&2}}^{out} + \Delta Q_{in_{b1&2}}^{out} - Q_{in_{b1&2}}^{out} \Delta C_{in_{b1&2}}^{out}$ for a priori known constant mixed venous conditions). During the inspiratory phase, with the descending profile, the rapid initial increase in $O_2$ tension accounts for the increase in $\phi_{O_2}$. As time elapses, the decrease in
FIG. 4. Time course of pulmonary blood flow descriptors. Regional alveolar resistive and compli-
ant properties are identical. Minute ventilation rate is set at 6 L/BTPS/min with a cycling frequency of 10 breaths/min and a duty cycle of 0.333. Ascending, descending, and square waveforms are denoted by a, d, and f, respectively, in the legend in all the panels.
FIG. 5. Time course of gas exchange during mechanical flow ventilation. Resistive and compliant properties of the individual alveolar regions are identical. Minute ventilation rate is set at 6 L(BTPS)/min with a cycling frequency of 10 breaths/min and a duty cycle of 0.333. Ascending, descending and square waveforms are denoted by a, d, and f, respectively, in the legend in all the panels.
perfusion rate compromises the increased \( O_2 \) tension; hence \( \phi_{O_2} \) falls accordingly (Fig. 5, bottom left). Analogous arguments can be made to explain the predicted results for the other flow waveforms. Performance is intermediate for the square profile. Exchange rate for \( CO_2 \) is more sensitive to the inspiratory waveform, compared to that for \( O_2 \), as the relative change in \( CO_2 \) content is much greater than for \( O_2 \). Note that the direction of changes in gas exchange rate for \( O_2 \) and \( CO_2 \) are in opposite directions. This is due to the concurrent effects of changing perfusion rate and change in species content. In a separate study (results not shown here), when capillary blood flow rate was presumed to be invariant with time (achieved by decoupling the circulation model), the time course of \( O_2 \) and \( CO_2 \) gas exchange rates qualitatively varied in a similar manner, both increasing in magnitude during the inspiratory phase and decreasing during the passive expiratory portion of the cycle.

4. Change in lumped thoracic compliance. Variations in thoracic volume during a respiratory cycle modulate the intrapleural pressure which, in turn, dictate gas exchange rates by manipulating inlet and outlet capillary perfusion rates. Figure 6 shows the effect of modifying assumed thoracic compliance on resulting cycle-averaged mixed arterial blood-gas values and total \( O_2 \) and \( CO_2 \) gas exchange rates. Decreasing thoracic compliance exaggerates variations in intrapleural pressure for similar excursions in alveolar inflation. An elevation in the mean intrapleural pressure ensues which, in turn, increases the nodal pressures in the pulmonary circulation leading to a concomitant reduction in blood perfusion rates through the pulmonary capillaries (Fig. 6, top). Although end-capillary species blood tensions do not change significantly with lowered \( C_{th} \) (scale exaggerates the slight differences calculated in Fig. 6, middle), the overall gas exchange rate falls with lowered thoracic compliance as a direct result of lowered perfusion rates Fig. 6, bottom). In all cases, a gradation based on the choice of the inspiratory waveforms is produced. As explained earlier, reduced perfusion during descending waveform overcomes increased oxygenation, resulting in \( O_2 \) exchange rates lower than that obtained during ascending waveform. For the case of \( CO_2 \) exchange, however, the change in \( CO_2 \) content (due to the higher slope of the \( CO_2 \) dissociation curve) effectively overrides the adverse effects of decreased perfusion. The net result then is an increase in \( CO_2 \) exchange with the descending waveform with increasing thoracic compliance.

5. Averaged effects. The previous sections indicate that the time courses are affected by the choice of the specific input inspiratory (and resulting expiratory) flow ventilatory waveforms. As depicted in Fig. 6, cycle-averaged quantities indeed result in observed differences, albeit to a smaller extent. End capillary blood oxygenation grades downward with descending, square, and ascending inspiratory flow waveforms, respectively. The effect on gas exchange is complex and is dictated by the concurrent effects of perfusion rates and extent of blood arterization. Perfusion and \( O_2 \) exchange are adversely affected by the descending waveform while proving favorable to blood gas composition and \( CO_2 \) excretion.

The ratio of regional ventilation to perfusion with the choice of inspiratory waveform was approximately the same for the various inspiratory waveforms. If
FIG. 6. Effect of thoracic compliance. Resistive and compliant properties of the individual alveolar regions were again identical. Minute ventilation rate was set at 6 L(BTPS)/min with a cycling frequency of 10 breaths/min and a duty cycle of 0.333. Ascending, descending, and square waveforms are denoted by a, d, and f, respectively, in all the panels.

The cycle-averaged value is defined as the ratio of the mean ventilation to mean perfusion rates, then the descending waveform had the highest value while the ascending waveform had the lowest value with an intermediate value obtained for the square waveform. During the inspiratory phase values of 3.45, 3.26, and 3.35 were obtained for the descending, ascending, and square waveforms, respectively.
The corresponding magnitudes during the expiratory phase were calculated to be 1.561, 1.558, and 1.559. The weighted mean average over the entire ventilatory cycle subsequently evaluated to 2.194, 2.124, and 2.156, respectively. These marginal differences in the averaged regional ventilation to perfusion ratios among the waveforms directly reflect the relatively small differences calculated for the net gas exchange rates of O_2 and CO_2. Experimental studies conducted on healthy anesthetized subjects concluded that any respiratory pattern that could provide sufficient alveolar ventilation would be adequate during artificial ventilation and the provision for using different respiratory waveforms seemed unnecessary (6).

Disparate Regional Ventilation

The effects of alterations in regional airway resistance or lung compliance parameters were studied to examine pathophysiological conditions. Maldistribution in ventilation results from temporal and spatial differences in the distribution of gas flow in the various units of the lung and leads to disparate regional gas exchange rates. Differences in regional ventilation were studied by altering either the R or C parameter values in one of the branches (affected alveolus) while maintaining the other branch (control alveolus) unmodified. When one of the branch resistances is increased, air flow through that branch is impeded during both the inspiratory and the expiratory phases, thereby prolonging both the filling and the emptying times. In due course this results in gas trapping, leading to CO_2 buildup with concomitant O_2 dilution in the affected alveolar region. Impeded airflow in the affected region, however, is compensated to some extent by hyperinflation in the control branch, leading to a better dilution of alveolar composition. When the compliances in the two branches are different, however, the more compliant alveolar region exhibits a larger volume change (alveolar hyperinflation) for similar changes in transmural pressure. Dilution of the alveolar gas with ambient air creates favorable transcapillary partial pressure gradients for both O_2 and CO_2.

Distribution of regional tidal volumes, peak alveolar pressures, mean perfusion rates, alveolar composition, and gas exchange rates is affected by spatial differences in resistance or compliance. One can track the distribution of ventilation by employing a compartmental dimensionless tidal volume ratio \( V_{TR} \), defined as the quotient of the tidal volumes of the control and affected branches. A value of unity represents uniform regional ventilation. Peak alveolar pressure ratio \( P_{PR} \) can also be similarly defined. Maldistribution in ventilation is then reflected in the distribution ratios diverging from unity. At low cycling rates, the divergence caused by compliance disparities is more significant when compared to that caused by resistive disparity. As depicted in Fig. 7, when branch resistances are unequal, use of the decelerating flow results in a more even distribution of tidal volumes and peak alveolar pressures when compared to that obtained with the ascending and square waveform. The decelerating waveform delivers the majority of ventilation during the early part of the respiratory cycle, thus favoring a more uniform distribution through extended equilibration times even when resistance was unilaterally increased (9). This would suggest that flow tapering inspiratory flows should be preferred in order to match regional resistive differences. On the other hand, with
FIG. 7. Effect of disparate regional resistive and compliance properties on regional distribution based on inspiratory waveform. Total minute ventilation rate was set at 6 L(BTPS)/min with a cycling frequency of 10 breaths/min and a duty cycle of 0.333 in all cases. [3R,C] denotes the case when $R_2 = 3R_1$ while $C_{A_2} = C_{A_1}$; [R,3C] denotes the case when $R_2 = R_1$ while $C_{A_2} = 3C_{A_1}$. 
a disparity in compliance, the ascending waveform provides a slightly better tidal volume distribution. Decelerating flow causes a larger portion of the delivered ventilation to be diverted to the more compliant region, further aggravating the maldistribution of ventilation. These predictions are qualitatively consistent with experimental observations conducted using a mechanical lung model (21) and in human patients under standard anaesthesia undergoing respirator therapy without heart or chest disease (25). Model calculations indicate marginal differences in regional perfusion with the descending profile, creating the greatest diversion in all cases. The effects on alveolar composition and total gas exchange rate are comparatively exaggerated in the case when compliance disparities exist when compared with resistive differences. This effect is solely the result of the cycling frequency as explained later.

Effects on overall gas exchange are summarized in Figs. 8 and 9. The decrement in perfusion rate caused by elevation in mean airway pressures during descending flow ventilation results in lower overall O2 exchange rates comparatively. The ascending flow facilitates better O2 exchange rate with the square waveform performing intermediate (Figs. 8 and 9, bottom left). In contrast, the descending flow best promotes better overall CO2 exchange. In one experimental study, 10 adult patients without known respiratory or cardiac disease were studied during anesthesia and artificial ventilation before elective surgery (26). Results indicated improved gas distribution with a decelerating flow pattern, but when the effects of gas exchange (measurements of oxygenation) were judged, greater benefits were obtained with accelerating flow.

Effect of Cycling Frequency

When the regional mechanical properties of the airways are dissimilar (as manifested by differences in the regional $R_j$ and/or $C_j$ values), the behavior of the overall system can be expected to vary with cycling frequency (36). Predicted effects on the distribution ratios are depicted in Fig. 10. When the regional mechanical properties are similar, all ratios are independent of frequency and trivially equal unity. Marked difference in the qualitative behavior of the system with frequency due to resistive (denoted by $3RC$ in Fig. 10) and compliance disparities (denoted by $R3C$) are observed. Increasing cycling frequency leads to an attenuation of the influence of compliance disparities (dashed-dot lines in Fig. 10). Resistive disparities, in contrast, are manifest at higher frequencies and lead to the distribution ratios deviating from unity at increasing frequencies. These results suggest that if achieving equilaterial lung performance is the goal, then it is beneficial to operate at low cycling frequencies in the presence of regional differences in airway resistance, whereas high-frequency ventilation would be the preferred mode when compliance disparities prevail.

Cycling frequency in fact governs the “effective” resistive and compliant load (or equivalently, “effective impedance”) offered to the ventilator by the respiratory system. Details about the derivation are furnished in Appendix B. In general, both effective resistance and compliance fall with increasing frequency, an observation consistent with earlier reports (14, 18, 36, 45). The general formulae for overall
FIG. 8. Effect of disparate regional resistances. Total minute ventilation rate was set at 6 L(BTPS)/min with a cycling frequency of 10 breaths/min and a duty cycle of 0.333 in all cases.
FIG. 9. Effect of disparate regional compliances. Total minute ventilation rate was set at 6 L(BTPS)/min with a cycling frequency of 10 breaths/min and a duty cycle of 0.333 in all cases.
FIG. 10. Effect of cycling frequency on regional distribution ratios during square wave inspiratory flow. Minute ventilation and duty cycle were held constant at 6 L (BTPS)/min and 0.333, respectively. The case when $R_2 = 3R_1$ is denoted by the dashed line, whereas the case when $C_{A2} = 3C_{A1}$ is denoted by the dashed-dot line in all the panels.
impedance pertaining to the model presented herein reduce to those reported by Otis et al. (36) when simplifying assumptions about gas incompressibility and thoracic compliance are invoked as demonstrated in Appendix B.

During homogeneous ventilation (figures not shown here), for the same minute ventilation rate, increasing cycling frequency results in smaller tidal volume displacement, increased perfusion rates, and lower arterial O2 and higher CO2 blood tensions. This results in a decrease in O2 and CO2 gas exchange performance with increasing frequency. The gradation based on inspiratory waveforms qualitatively resembles that observed in Fig. 6. Effects of increasing cycling frequency while maintaining the minute ventilation unchanged are summarized in Fig. 11 during square wave ventilation. Despite the higher mean perfusion rate obtained at increased cycling frequency, the significant inefficiency in arterialization (low O2 and high CO2 blood tensions depicted in the Fig. 11 (middle)) results in poorer performance with respect to overall gas exchange rates.

Effect of imposed (extrinsic) PEEP

Figure 12 depicts the effects of externally applying progressive levels of PEEP (viz., 5 and 10 cm H2O, respectively). Elevation in the levels of PEEP lead to an increase in mean alveolar and airway pressures and functional residual capacity which, in turn, lead to a reduction in the rate of perfusion through the capillary when Pa and Pv are maintained constant. Reduction in perfusion with PEEP leads to a significant decrement in overall gas exchange rate of both O2 and CO2. Increasing alveolar volumes result in diluting alveolar contents with ambient air, ultimately leading to improvements in arterial oxygenation of blood as indicated by the gradation in alveolar composition.

Effect on Expired Gases

The time course of expired gas concentrations is generally insensitive to the choice of the inspiratory flow profile, all other conditions being the same. All results presented here are for the square inspiratory flow waveform. Figure 13 depicts contrasting behavior observed in the tracings of the expired gas concentration under different conditions. In the top panels, increasing endotracheal tube resistance mainly affects the initial upstroke slope of the capnogram (or correspondingly, the initial downstroke on the oxigram). Increasing airway resistance mainly hinders flow during expiration, affecting the rate of emptying of alveolar contents. This is directly reflected in the observed slopes in the capnogram. End-tidal compositions are marginally affected as the alveolar contents are effectively exhausted to the ambient at the end of the expiratory phase. In contrast, in the bottom panels, increasing the level of external PEEP affects gas exchange rates significantly. Gas exchange rate and hence alveolar composition is directly affected. This is now directly reflected in the gas composition obtained at end-tidal conditions. Note the gradation with levels of external PEEP depicted in Fig. 13.

DISCUSSION

The model presented in this paper includes a concurrent description of respiratory mechanics, pulmonary blood flow, and gas exchange to examine the effects of
FIG. 11. Effect of cycling frequency on overall gas exchange during square wave inspiratory flow with branch resistive disparities. Minute ventilation and duty cycle were held constant at 6 L [BTPS]/min and 0.333, respectively.
FIG. 12. Effect of extrinsically imposed PEEP on alveolar composition, perfusion and gas exchange while employing a flat inspiratory flow ventilation. A cycling frequency of 12 breaths/min (with minute ventilation of 6 L [BTPS]/min and a duty cycle of 0.4) was maintained in all cases. Regional resistance and compliance values were the same and equal to the nominal values as indicated in Table 1.

altering ventilation on capillary blood flow rate and ensuing gas exchange. This coupled interaction has not been previously addressed in theoretical studies on mechanical ventilation.

Model predictions indicate that when symmetric regional ventilation is considered, the choice of the pattern of inspiratory flow affects the time course of $O_2$
FIG. 13. Effect of changing conditions on expired gas composition while employing a square wave inspiratory flow ventilation. A cycling frequency of 12 breaths/min (with minute ventilation of 6 L [BTPS]/min and a duty cycle of 0.4) was maintained in all cases. Regional resistance and compliance values were the same and equal to the nominal values as indicated in Table 1. (A) Effect of endotracheal tube resistance. (B) Effect of externally imposed PEEP.
and CO₂ alveolar composition, capillary perfusion, and gas exchange rates (Figs. 3, 4, and 5). Descending waveform yields the highest cycle-averaged airway, intrapleural and alveolar pressures while the ascending waveform yields the lowest values. In contrast, mean capillary perfusion rate is greatest during ascending flow and lowest during descending flow. Mean end capillary blood gas tension do not significantly change with choice of the inspiratory waveform. However, the combined effect due to perfusion discrepancies subsequently result in changes in gas exchange rates. The descending waveforms favor CO₂ exchange while the ascending waveform favors O₂ exchange. Reduced thoracic compliance exaggerates variations in intrathoracic pressures, which significantly decrease capillary perfusion rates, leading to deleterious effects on O₂ and CO₂ gas exchange rates (Fig. 6). The square waveform grades in between throughout the study.

Parameters affecting the mechanical behavior of the lungs and/or regional ventilation (such as airway resistance and alveolar compliance) determine the extent to which ventilation affects gas exchange. Alterations in inspiratory waveforms would be expected to significantly affect the instantaneous V/Q ratios with concomitant effects on regional alveolar gas partial pressures and end-capillary blood tensions. Computed results presented here indicate that regional alveolar partial pressures track the cycle-averaged V/Q, thereby attenuating the effects of significantly larger intracycle V/Q variations. This is, in large part, due to the capacitance of the alveolar compartments. Our finding that descending flow facilitates the most even distribution of ventilation is in line with other reports (21, 23, 25, 27). The peak alveolar pressure distribution ratio, P_TR, is the lowest with descending flow even during heterogeneous alveolar ventilation (Fig. 7).

Differences in regional distribution ratios vary significantly with cycling frequency. Inequalities in compliance yield pronounced effects on net gas exchange rates at low frequencies of operation, whereas the adverse effects of inequalities in resistance are more pronounced at higher frequencies (Fig. 10). One convenient way of evaluating the effects of airway mechanics on distribution of ventilation has been to employ RC time constants (3). While alterations in regional time constants as a consequence of differences in regional airway resistance and/or alveolar compliance do affect distribution of ventilation, they do not include the effects of airway mechanics on regional perfusion and thus are inadequate to evaluate the effects of different inspiratory waveforms on gas exchange.

Application of extrinsic PEEP elevates mean intrathoracic pressures, thereby adversely affecting overall pulmonary perfusion. This results in reduced gas exchange performance in spite of dilution of alveolar contents because of increased alveolar volume (Fig. 12). Time course of expired gas concentration is dictated by the combined effects of gas exchange rate and expiratory air flow rate. Factors that lead to a reduction in expiratory airflow rate alone result in lowering of the initial upstroke of the capnogram (or, correspondingly the initial downstroke of the oxigram). End-tidal values for CO₂ change proportionally with CO₂ exchange rates and inversely with O₂ exchange rates (Fig. 13).

The model on the air-side comprised an upper airway compartment connected to the alveolar region through a serial-parallel arrangement of peripheral airways.
Alternate descriptions using a nonlinear model including the use of a mid airway collapsible segment have been employed to describe the mechanics of airflow (5). A collapsible segment is necessary to describe airway closure due to large positive intrapleural pressures occurring during forced expiration. In a recent study, describing the dynamics of the forced vital capacity maneuver necessitated the use of a collapsible segment (31). In the study presented in this paper, a linear pressure-volume relationship (thereby implying a constant alveolar compliance) was employed to characterize the comparatively small excursions in lung volume and intrapleural pressures encountered during mechanical ventilation.

Model Limitations

The analysis presented must be considered within the context of several model limitations:

1. The use of a lumped model precludes an accurate depiction of time delays in the capnogram.
2. The description of pulmonary blood flow ignores gravitationally induced changes in hydrostatic pressures. The use of constant pressure sources to depict pulmonary arterial and venous pressures ignores the pulsatile blood flow caused by pumping action of the right ventricle and left atrium as well as compensatory changes in arteriolar and venous pressures. Compensatory effects on pulmonary arterial pressure resulting from changes in pulmonary resistance are not considered. Furthermore, modulation of pulmonary vascular resistance by O2 tension in blood (33, 35) has also been neglected.
3. The potential effects of PEEP on alveolar recruitment as would be expected in patients with atelectasis (or shunt) are ignored.
4. Absence of inertial elements in the model limit its consideration to relatively low frequencies. Investigation of higher frequencies must necessarily include inertia elements.
5. Changes in alveolar and blood gas composition are assumed to be caused by the effects of ventilation and perfusion at the level of the alveolar capillary. Mixed venous composition of blood entering the capillary bed is assumed to be constant. Hence the predicted results are strictly applicable only for the evaluation during open-loop conditions.

CONCLUSIONS

Countering effects describe the interaction between respiratory mechanics and perfusion on gas exchange during mechanical ventilation. Lung inflation decreases blood flow through the pulmonary capillaries. This is an important factor while evaluating the potential benefit of a certain type of gas flow pattern during respiratory treatment. The cumulative effect on gas exchange rate is mixed because of the opposing outcomes of ventilation on perfusion. For instance, although the descending waveform promotes blood arterialization, the ensuing reduction in perfusion rate dominates, thereby tending to decrease O2 exchange rate. In contrast, with the ascending flow pattern, a higher mean perfusion rate prevails, thus yielding
a higher $O_2$ exchange rate across the capillary in comparison. The effect on $CO_2$ exchange rate is dictated by the nature of the $CO_2$ blood dissociation curve; in the regime of normocapnic operation, the larger slope of the dissociation curve mandates large changes in $CO_2$ content for slight changes in blood $CO_2$ tension. This overrides the benefits of improved perfusion during ascending flow. The descending waveform promotes better exchange rates with ascending flow trailing the list among the waveforms investigated.

However, if the gas exchange rate that is time-averaged over the course of a respiratory cycle is to be considered as the criterion for defining ventilator performance, no discernable (hence clinically significant) difference can be reported while comparing the various forms of inspiratory airflow. This remark holds true even for the scenario when RC mismatches were considered. Generally, the performance of the flat and sinusoidal waveforms graded between that of descending and ascending flows. In addition, regional pressures and ventilatory dynamics cause significant effects on regional gas exchange rates.

Modulation of cycling frequency yields contrasting behavior. Time constant discrepancies yield proportionate changes in the impedances of the separate pathways. The volume-elastic and flow-resistive properties are different, however. At lower frequencies, effective branch impedances are mainly influenced by the compliant properties, manifested by compliant disparities significantly affecting regional ventilation, alveolar species composition, and ensuing gas exchange at low frequencies. Resistive disparities are more apparent at higher frequencies, however.

The importance of considering the concomitant effects of perfusion on gas exchange is readily apparent. Increasing intrapleural pressure (due to either extrinsic/auto PEEP or impeded movement of the chest wall) results in decreased and, hence, unfavorable perfusion rates leading to decrements in gas transfer.

APPENDIX A

Model equations are developed by employing macroscopic balances on the overall mass, overall linear momentum and species mass in predefined control volumes representing the anatomic dead space and the individual alveolar regions. Air is assumed to behave ideally with its overall mass density ($\rho$) being defined by a (constitutive) ideal gas law equation of state, $P = \rho RT/M$, where $R$ is the universal gas constant. Changes in density of air throughout the system are therefore accounted for and governed by the corresponding changes in the total pressure in the various nodal point regions. The molecular weight of air, $M$, is presumed to be invariant to changes in air composition in the ensuing formulation.

(I) Mechanics

Air-side. The dynamic equations for the total pressure and volume in the $N$ alveolar regions ($P_A$ and $V_A$ for the $j$th region respectively) and the resulting intrapleural pressure ($P_{PL}$) can be written compactly as
$$\begin{array}{ccccc}
1 & \cdots & 0 & \frac{V_{A1}}{P_{A1}} & 0 \\
i & \cdots & i & \cdots & i \\
0 & \cdots & 1 & 0 & \frac{V_{AN}}{P_{AN}} \\
\end{array} \quad \frac{dV_{A1}}{dt} \begin{bmatrix}
\Psi_1 \\
\vdots \\
\Psi_N \\
\end{bmatrix} = 0 \quad \text{[1]}
\end{array}$$

\[
\begin{bmatrix}
\frac{1}{C_{A1}} & \cdots & 0 & 1 & \cdots & 0 & -1 \\
i & \cdots & i & \cdots & i & \cdots & i \\
0 & \cdots & \frac{1}{C_{AN}} & 0 & \cdots & 1 & -1 \\
\end{bmatrix} \quad \frac{dP_{A1}}{dt} \begin{bmatrix}
\frac{dP_{AN}}{dt} \\
\vdots \\
\frac{dP_{PL}}{dt} \\
\end{bmatrix} = 0
\]

where $C_{Aj}$ is the compliance of the alveolar region $j$ and $C_{th}$ is the compliance of the thorax. In general, these compliances can be nonlinear. The above representation lends itself to easy extension for the general case of considering $N$ parallel alveolar regions in the model. The form of $\Psi_j$ for region $j$ differs during inspiration and expiration and is given as

\[
\Psi_j = \frac{P_D}{P_{A_j}} Q_{D_{A_j}} - \frac{P_s T_B}{T s P_{A_j}} \Phi^{\text{TOT}_j}_j \text{ during inspiration} \quad \text{[2a]}
\]

\[
\Psi_j = -Q_{AD_j} - \frac{P_s T_B}{T s P_{A_j}} \Phi^{\text{TOT}_j}_j \text{ during expiration,} \quad \text{[2b]}
\]

where $P_D$ is the total pressure in the dead space. $\Phi^{\text{TOT}_j}_j$ is the total rate of gas exchange of O$_2$, CO$_2$, and N$_2$ across the alveolar–capillary barrier in alveolar space $j$ and is given as

\[
\Phi^{\text{TOT}_j}_j = \sum_{i=1}^{N_{\text{TOT}}} (Q_{b_{ij}} C_{b_{ij}}^{\text{out}} - Q_{b_{ij}} C_{b_{ij}}^{\text{in}}). \quad \text{[3]}
\]

The summation represents the total transfer rate (STPD) of all species $i$ across the capillary wall in alveolar space $j$. The corresponding dynamic equation in the dead space region is written as

\[
\frac{dP_D}{dt} = \frac{1}{V_D} \left[ P_E Q_{ED} + \sum_{j=1}^{N_{\text{TOT}}} (Q_{AD_j} P_{A_j} - Q_{D_{A_j}} P_D) \right] \text{ during inspiration} \quad \text{[4a]}
\]
\[
\frac{dP_D}{dt} = \frac{1}{V_D} \sum_{j=1}^{N} (Q_{AD_j} P_{A_j} - Q_{DA_j} P_D) - Q_{DE} P_D
\]
during expiration. \[4b\]

The summations in Eqs. [4a] and [4b] account for the cases when inspiration and expiration in the individual alveolar regions do not occur in synchrony, thereby resulting in pendelluft flow between the alveolar regions. At any point in time in any alveolar branch \( j \), only one of the flows \( Q_{DA_j} \) or \( Q_{AD_j} \) will be nonzero. All flows listed above are derived from the balance of overall linear momentum in each region and are evaluated at body temperature. Ignoring the inertial contributions (20) the expressions for flow in the various regions are given as

\[
Q_{ED} = \frac{P_E - P_D}{R_{UAW}} \quad [5a]
\]
\[
Q_{DA_j} = \frac{P_D - P_{A_j}}{R_j} \quad [5b]
\]
\[
Q_{DE} = \frac{P_D - P_E}{R_{UAW}} \quad [5c]
\]
\[
Q_{AD_j} = \frac{P_{A_j} - P_D}{R_j}. \quad [5d]
\]

The resistances, \( R_{UAW} \) and \( R_j \), in general, can take different values during the inspiratory and expiratory phases.

**Blood-side.** The pulmonary vasculature is partitioned into (i) extraalveolar pulmonary arterial and venous compartments whose volumes are modulated by the intrapleural pressure and (ii) intraalveolar regional capillary compartments whose volumes are modulated by the corresponding regional alveolar pressure. The resistance to flow through each of the compliant compartments is described using a Starling resistor type relationship and is a function of the corresponding compartmental volume. Mean pulmonary arterial and venous hydrostatic pressures \( P_{pa} \) and \( P_{pv} \), respectively) are assumed to be constant and are denoted by constant pressure sources of 15 and 5 mm Hg relative to the intrathoracic pleural pressure, respectively. Pulsatile effects resulting from the pumping of the right ventricle during the cardiac cycle are hereby ignored. The corresponding dynamic equations are given as

\[
P_a = P_{TMa} + P_{PL} \quad [6a]
\]
\[
P_j = P_{TMb_j} + P_{A_j} \quad [6b]
\]
\[
P_v = P_{TMv} + P_{PL} \quad [6c]
\]
\[ R_a = R_{a0} \left( \frac{V_{\text{max}}}{V_a} \right)^2 \]  
[6d]

\[ R_{c_j} = R_{c_j0} \left( \frac{V_{\text{max}}}{V_{b_j}} \right)^2 \]  
[6e]

\[ R_v = R_{v0} \left( \frac{V_{\text{max}}}{V_v} \right)^2 \]  
[6f]

\[ \frac{dV_a}{dt} = \frac{(P_{pa} - P_{TMa})}{R_a} - \sum_{j=1}^{N} \frac{(P_a - P_{c_j})}{R_{c_j}/2} \]  
[6g]

\[ \frac{dV_{b_j}}{dt} = \frac{(P_a - P_{c_j})}{R_{c_j}/2} - \frac{(P_{c_j} - P_{c_j})}{R_{c_j}/2} \]  
[6h]

\[ \frac{dV_v}{dt} = \sum_{j=1}^{N} \frac{(P_{c_j} - P_v)}{R_{c_j}/2} - \frac{(P_{TMv} - P_{pv})}{R_v} \]  
[6i]

where the subscript \( j \) again indicates the region perfusing alveolar compartment \( j \). In Equations [6g], [6h], and [6i] blood flow through the pulmonary circulation is implicitly assumed to be incompressible. Perfusion through the capillary bed (\( Q_{in}^{b_j} \) and \( Q_{out}^{b_j} \), respectively) is governed by the gradient in the regional nodal pressures listed in Eqs. [6a] through [6c]. Blood flow entering and leaving the capillary bed (\( Q_a \) and \( Q_v \), respectively) is similarly dictated by the corresponding nodal pressure gradients. Ignoring inertial contributions once again, expressions for the regional blood flow rates are listed below:

\[ Q_{in}^{b_j} = \frac{(P_{pa} - P_{c_j})}{R_{c_j}/2} \]  
[7a]

\[ Q_{out}^{b_j} = \frac{(P_{c_j} - P_v)}{R_{c_j}/2} \]  
[7b]

\[ Q_a = \frac{(P_{pa} - P_{TMa})}{R_a} \]  
[7c]

\[ Q_v = \frac{(P_{TMv} - P_{pv})}{R_v} \]  
[7d]

(II) Gas Exchange

Species mass balance equations describing the change in partial pressure of species \( i \) in the airways (assumed well-mixed) can be written separately for the inspiratory and expiratory phases as (subscript denoting alveolar region \( j \))
Inspiration

\[
\frac{dP_{D_i}}{dt} = \frac{1}{V_D} \left( Q_{ED} P_{E_i} + \sum_{j=1}^{i=N} (Q_{AD} P_{A_j} - Q_{DA} P_{D_j}) \right) \tag{8a}
\]

\[
\frac{dP_{A_j}}{dt} = \frac{1}{V_{A_j}} \left[ Q_{DA} P_{D_i} - P_{A_j} \frac{dV_{A_j}}{dt} - \frac{(P_S T_B)}{T_S} \phi_{ij} \right] \tag{8b}
\]

Expiration

\[
\frac{dP_{D_i}}{dt} = \frac{1}{V_D} \left[ \sum_{j=1}^{i=N} (Q_{AD} P_{A_j} - Q_{DA} P_{D_j}) - Q_{DE} P_{D_i} \right] \tag{9a}
\]

\[
\frac{dP_{A_j}}{dt} = \frac{1}{V_{A_j}} \left[ -Q_{AD} P_{A_j} - P_{A_j} \frac{dV_{A_j}}{dt} - \frac{(P_S T_B)}{T_S} \phi_{ij} \right]. \tag{9b}
\]

where \( \phi_{ij} \), given by \([Q^{\text{out}}_{bj} C^{\text{out}}_{bj} - Q^{\text{in}}_{bj} C^{\text{in}}_{bj}] \), represents the gas exchange rate of species \( i \) across the lumped capillary perfusing alveolar region \( j \). End-capillary equilibration with alveolar composition is assumed; hence the species tension of blood leaving the capillary, \( P_{ec_{ij}} \), is assumed to equal the alveolar species partial pressure, \( P_{A_{ij}} \). The formulation for gas exchange as presented herein then cannot be applied to address the scenario of diffusion impairment across the alveolar capillary barrier.

**APPENDIX B**

The driving point impedance on the air side for the system presented in this paper defines the effective “load” to the ventilator and can be derived easily by determining the equivalent admittance and subsequently carving out the real and imaginary parts. The process yields the equivalent resistance and compliance as

\[
R_{\text{equiv}} = R_{UA} W + \frac{1}{\alpha(\lambda_a^2 + \lambda_b^2)} (\mu_a \lambda_a + \mu_b \lambda_b) \tag{10a}
\]

\[
C_{\text{equiv}} = \frac{-(\lambda_a^2 + \lambda_b^2)}{(\mu_a \lambda_a - \mu_b \lambda_b)}, \tag{10b}
\]

where the terms \( \lambda_{a,b} \) and \( \mu_{a,b} \) themselves are implicit functions of \( C_1, C_2, C_0, C_{gu}, C_{g1}, C_{g2}, \tau_1, \tau_2 \) and the cycling frequency, \( \omega \) (in radians). The regional time constants, \( \tau_j \) are defined as \( \tau_j = R_j C_j \). The terms \( \lambda_{a,b} \) and \( \mu_{a,b} \) indicated in Eqs. [10a] and [10b] are defined as
\[
\mu_a = \omega C_1 C_2 [\tau_1 C_1 + \tau_2 C_2 + C_{th}(\tau_1 + \tau_2)] \\
+ \omega (C_1 + C_2 + C_{th}) [\tau_1 C_2 C_{g1} + \tau_2 C_2 C_{g2}] \\
\mu_b = -C_1 C_2 (C_1 + C_2 + C_{th}) + \omega^2 \tau_1 \tau_2 [C_1 C_2 C_{g1} + C_{g2}] + C_{g1} C_{g2} (C_1 + C_2) \\
+ \omega^2 \tau_1 \tau_2 C_{th} (C_1 + C_{g1}) (C_2 + C_{g2}) \\
\lambda_a = C_1 C_2 [(C_1 + C_2 + C_{th})(C_{gu} + C_{g2}) + C_{th}(C_1 + C_2)] \\
- \omega^2 \tau_1 \tau_2 C_{gu} C_{th} (C_1 + C_{g1}) (C_2 + C_{g2}) \\
- \omega^2 \tau_1 \tau_2 C_{gu} [C_{g1} C_{g2} (C_1 + C_2) + C_1 C_2 (C_{g1} + C_{g2})] \\
\lambda_b = \omega C_{gu} C_{th} [\tau_1 C_2 C_{g1} + \tau_2 C_1 C_{g2} + C_1 C_2 (\tau_1 + \tau_2)] \\
+ \omega C_{gu} [C_1 C_2 (\tau_1 C_1 + \tau_2 C_2 + \tau_1 C_{g1} + \tau_2 C_{g2} + \tau_1 C_2 C_{g2} + \tau_1 C_2 C_{g1}] \\
+ \omega C_{th} [\tau_1 (C_1 + C_{g1}) (C_2 + C_{g2})] \\
+ \omega C_{g1} C_{g2} [C_1 C_2 (C_1 + C_{g1})] \\
\] [11a]

If gas flow is assumed to be incompressible, the above expressions are simplified by evaluating the limiting expressions as \( C_{g1}, C_{g2}, \) and \( C_{gu} \) all \( \rightarrow \) zero. This would result in the following modified expressions

\[
\overline{R}_{\text{equiv}} = R_{UAW} + \frac{(\tau_1 C_1 + \tau_2 C_2) + \omega^2 \tau_1 \tau_2 (\tau_1 C_2 + \tau_2 C_1)}{(C_1 + C_2)^2 + \omega^2 (\tau_1 C_2 + \tau_2 C_1)^2} \\
\overline{C}_{\text{equiv}} = \frac{(C_1 + C_2)^2 + \omega^2 (\tau_1 C_2 + \tau_2 C_1)^2}{(C_1 + C_2)^2 + \omega^2 (\tau_1 C_2 + \tau_2 C_1)^2} \\
\] [12a]

Furthermore, if the thoracic compliant element is completely ignored (by setting \( C_{th} \rightarrow \infty \)), Eqs. [12a] and [12b] may be further simplified. The resulting expressions (when \( R_{UAW} = 0 \)) would then correspond with those reported in Otis et al. [36] and elsewhere [10]. The equivalent resistance and compliance diminish with cycling frequency and approach specific limits at the extremes of frequency.

**APPENDIX C**

Empirical dissociation curves based on previously reported studies (15, 28, 32, 41) were employed to relate species contents to the equilibrium gas tensions in the equations describing gas exchange in Appendix A. The relationship between the gas tensions and species contents is complex and nonlinear. The first stage of the calculation procedure involves the following series of calculations:
\begin{align*}
\text{pH}^* &= 7.59 - 0.2741 \log \left( \frac{P_{CO_2}}{20} \right) \tag{13a} \\
dT &= 37 - T \tag{13b} \\
dpH &= 7.4 - \text{pH}^* \tag{13c} \\
dpCO_2 &= 40/P_{CO_2} \tag{13d} \\
\Omega &= 0.024 \ dT - 0.4 \ dpH + 0.06 \log 10(dpCO_2) \tag{13e} \\
X &= P_{O_2} \ 10^\Omega \ \frac{26.8}{26.8 + DP50} \tag{13f} \\
SO_2 &= \frac{X^3 + 150X}{X^3 + 150X + 23400} \tag{13g} \\
Y &= 3 \times 10^{-5} \ Hb \ (1 - SO_2) \tag{13h} \\
\text{pH} &= 7.59 + Y - 0.2741 \log \left( \frac{P_{CO_2}}{20} \right). \tag{13i}
\end{align*}

Equation [13a] is used to first guesstimate pH. Next, for a given temperature ($T$ in Eq. [13b]) and known values of hemoglobin concentration (Hb), 2–3 DPG shift factor (DP50) and base excess (BE), Eqs. [13c] through [13i] are iteratively solved till a convergent value for pH is obtained. The resulting oxygen saturation (SO$_2$) so obtained is then used to determine blood O$_2$ content as explained below. $X$ denotes virtual $P_{O_2}$ used to calculate oxygen saturation levels using a standardized dissociation curve correlation. In the second stage, the following set of calculations are performed:

\begin{align*}
pKp &= 6.086 + 0.042 \ dpH + (38 - T)(0.00472 + 0.00139 \ dpH) \tag{14a} \\
a_{CO_2} &= 0.0307 + 0.00057 \ dT + 2 \times 10^{-5} \ dT^2 \tag{14b} \\
\Delta_1 &= 0.02226a_{CO_2}P_{CO_2}(1 + 10^{(pH-pKp)}) \tag{14c} \\
\Delta_2 &= 1 - \frac{0.02924 \ Hb}{(2.244 - 0.422 \ SO_2)(8.74 - \ pH)}. \tag{14d}
\end{align*}

Finally, blood species contents (in units of ml (STPD) per ml blood) are determined using

\begin{align*}
C_{bo2} &= 1.39 \ Hb \ \frac{SO_2}{100} + 3 \times 10^{-5} \ P_{O_2} \tag{15a} \\
C_{bco2} &= \Delta_1 \times \Delta_2. \tag{15b}
\end{align*}
Throughout this study, all variations in blood-gas tensions were assumed to be directly attributed solely to respiratory effects with no compensatory metabolic mechanisms. Hemoglobin concentration was assumed to be equal to 14.46 g/100 ml blood and DP50 was assumed to be zero.

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