A Mathematical Model of Air-Flow Induced Regional Over-Distention during Mechanical Ventilation: Comparing Pressure-Controlled and Volume-Controlled Modes

P.S. Crooke*, A.M. Kaynar, and J.R. Hotchkiss

Abstract. In this paper we study a five compartment lung model to examine the effects of heterogeneity (*i.e.*, different portions of the lungs have different impedance characteristics) on physiologic outcomes using two common modes of mechanical ventilation: pressure-controlled (PCV) and volume-controlled (VCV). In particular, we attempt to answer the question: If heterogeneity exists in the lungs, then does one mode produce lower peak alveolar pressures, given a desired overall tidal volume? A third type of mechanical ventilation, decelerating flow ventilation (DFV), is also considered and it is shown that an optimal initial flow (a multiple of the desired minute ventilation) exists that will minimize peak compartmental pressures.

Keywords: model, mechanical ventilation, mutli-compartment, pressure-controlled ventilation, volume-controlled ventilation, decelerating flow ventilation.

AMS Classification: 92C30, 92C50.

1 Introduction

Mechanical ventilation can–by itself–damage the lungs. This contention is supported by many experiments in animals (see [1]). Elegant experimental work indicates that airspace overdistention (*i.e.,* volutrauma), rather that

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elevated distending pressures (*i.e.,* barotrauma) *per se*, causes the injury [2]. Clinical studies are also consistent with the hypothesis that airspace overdistention during mechanical ventilation is injurious ([3, 4]). Restricting the tidal volume (V_T) during mechanical ventilation decreases mortality in Acute Respiratory Distress Syndrome (ARDS), as well as the risk of acute lung injury in other settings ([5]). Animal studies [6] have demonstrated the ventilatory-induced lung injury (VILI) is regionally heterogeneous and correlates with cyclical airway collapse and recruitment.

Disease/injured lungs are mechanically heterogeneous, both in the setting of ARDS and in the context of Chronic Obstructive Pulmonary Disease (COPD). Interaction between the applied pattern of ventilation and mechanical heterogeneity would be expected to cause differences in the peak strains (*i.e.,* peak airspace volumes) among different regions of the lungs. In the clinical setting, we can only control global strain during volume controlled ventilation (VCV) by changing tidal volume and/or positive end expiratory pressure (PEEP). During pressure controlled ventilation (PCV), we can only control global peak stress via modification of set inspiratory pressures and PEEP. Moreover, the outcome of our interventions can only be measured as global strain during VCV or global stress during PCV. Apart from global measures of stress and strain during mechanical ventilation, we cannot infer regional stresses or strains in the clinical setting using currently available methods. This may lead to unrecognized overdistention and subsequent injury in mechanically ventilated patients.

During VCV, one of the commonly referred guides is to restrict peak pressures along with tidal volumes, thus lessening the risk of lung injury ([7, 8]). However, analysis of neither experimental nor clinical data could not identify a *break point* in peak pressures below which restricting the tidal volume no longer decreased adverse consequences([9, 10]).

In this *in silco* study, we used a mathematical model to evaluate the hypothesis that VCV increases the incidence of regional overdistention as compared to PCV. This topic has recently been investigated from a clinical perspective ([11–15]). The model allows one to explore the magnitude of potential heterogeneity in peak regional strains during volume controlled as compared to pressure controlled ventilation. We also investigated the sensitivity with which common clinical measures would be expected to detect elevated regional strains. The *in silico* approach permits more detailed examination of a greater number of impedance configurations than would be practical in the experimental or laboratory settings.

2 The Mathematical Model

Mathematical models ([16, 17]) have been developed to predict clinical outcomes such as tidal volumes, mean alveolar pressures, end-expiratory pressures, given the physiologic parameters of the patient and the ventilator

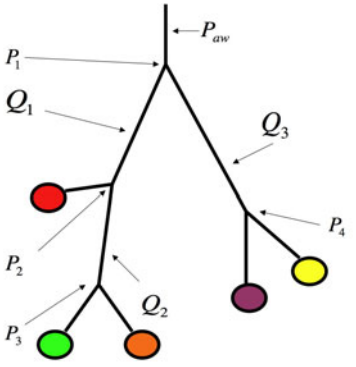

Fig. 1. Model lung configuration

settings. Some models ([19]) have incorporated two heterogeneous compartments (*i.e.,* two compartments with different compliances and resistances). To approximate the notion of heterogeneity of the lungs, our model is composed of five compartments as depicted in Figure 1. Each compartment has separate impedance characteristics. We studied the compartmental volumes over one cycle of mechanically controlled breathing which is composed of two segments: inspiration and expiration. The time of one cycle is denoted by t_{tot}. Inspiration occurs during the time-interval, $0 \leq t \leq t_i$ and expiration during $t_i \leq t \leq t_{tot}$. For PCV, we control the airway pressure (P_{aw}) and assume that during inspiration, $P_{aw} \equiv P_{set}$, $0 \leq t \leq t_i$. For VCV, the airway flow (Q_{aw}) is controlled during inspiration. The assumptions for expiration are identical in either mode of ventilation, namely, $P_{aw} \equiv P_{PEEP}$, $t_i \leq t \leq t_{tot}$.

The mathematical model for the five compartments as shown in Figure 1 is constructed using pressure and flow balances at junction points and along segments that are depicted in Figure 2. To illustrate the construction of the model, we consider the balances in the pressure controlled case when $P_{aw}(t) \equiv P_{set}$. In the compartments (A,B,C,D,E), the compliance of each compartment is denoted by C_j, the resistances by R_j, and end-expiratory pressures by P_{ex_j}. The pressure in each compartment is the sum of resistive (R_jQ_j), elastic (V_j/C_j) and residual (P_{ex_j}) where V_j is the instantaneous compartment volume and $Q_j = dV_j/dt$ is the flow in or out of the compartment. The resistances along the three connection segments are denoted by R_{LTR}, R_{LBR}, and R_{RMR}. Using this information, the following 13 equations involving the unknown compartment volumes (V_j) and compartment flows (dV_j/dt) are used to develop the system of differential equations for the compartmental volumes:

where $\tilde{P}_j^{(i)}$ depends on the end expiratory pressure (P_{ex_j}) and the airway pressure (P_{set}). The coefficients ($\alpha_j^{(i)}$, $\beta_j^{(i)}$, $\gamma_j^{(i)}$, $\delta_j^{(i)}$, and $\epsilon_j^{(i)}$) of the compartmental volume terms depend on the physiologic parameters (compliance and resistance of each compartment). The superscript on these constants, (i), denote the values of these constants during *inspiration*. At the start of inspiration we assume the compartmental volume is measured from its residual volume (P_{ex_j}/C_j) and hence, we assume $V_j^{(i)}(0) = 0$, $j = A, B, C, D, E$, which provide the initial conditions for the system of differential equations. We note that at this point in the model development, the end expiratory pressures are unknown. They will be determined after the expiratory part of the model is solved. We denote the solutions of (2) as $V_j^{(i)}(t)$, $0 \le t \le t_i$, $j = A, B, C, D, E$.

Using the same pressure and flow balance equations as in (1), except that we have $P_{aw} = P_{peep}$, $t_i \le t \le t_{tot}$, the corresponding system of differential equations can be obtained for the volumes in each compartment during expiration. In particular, we find:

$$\begin{aligned}
dV_A^{(e)}/dt &= \alpha_A^{(e)}V_A^{(e)} + \alpha_B^{(e)}V_B^{(e)} + \alpha_C^{(e)}V_C^{(e} + \alpha_D^{(e)}V_D^{(e)} + \alpha_E^{(e)}V_E^{(e)} + \tilde{P}_A^{(e)} \\
dV_B^{(e)}/dt &= \beta_A^{(e)}V_A^{(e)} + \beta_B^{(e)}V_B^{(e)} + \beta_C^{(e)}V_C^{(e)} + \beta_D^{(e)}V_D^{(e)} + \beta_E^{(e)}V_E^{(e)} + \tilde{P}_B^{(e)} \\
dV_C^{(e)}/dt &= \gamma_A^{(e)}V_A^{(e)} + \gamma_B^{(e)}V_B^{(e)} + \gamma_C^{(e)}V_C^{(e)} + \gamma_D^{(e)}V_D^{(e)} + \gamma_E^{(e)}V_E^{(e)} + \tilde{P}_C^{(e)} \\
dV_D^{(e)}/dt &= \delta_A^{(e)}V_A^{(e)} + \delta_B^{(e)}V_B^{(e)} + \delta_C^{(e)}V_C^{(e)} + \delta_D^{(e)}V_D^{(e)} + \delta_E^{(e)}V_E^{(e)} + \tilde{P}_D^{(e)} \\
dV_E^{(e)}/dt &= \epsilon_A^{(e)}V_A^{(e)} + \epsilon_B^{(e)}V_B^{(e)} + \epsilon_C^{(e)}V_C^{(e)} + \epsilon_D^{(e)}V_D^{(e)} + \epsilon_E^{(e)}V_e^{(e)} + \tilde{P}_E^{(e)}
\end{aligned} \tag{3}$$

where $\tilde{P}_j^{(e)}$ depends on P_{ex_j} and the applied PEEP (P_{PEEP}). The initial conditions for (3) are $V_j^{(e)}(t_i) = V_j^{(i)}(t_i)$ and the resulting solutions of this initial-value problem are denoted as $V_j^{(e)}(t)$, $t_i \le t \le t_{tot}$.

Having the solutions of (2) and (3), the end-expiratory pressures for each compartment can be determined by requiring that $V_j^{(e)}(t_{tot}) = 0$ for $j = A, B, C, D, E$. This is accomplished by solving a linear system of algebraic equations for $P_{ex_A}, P_{ex_B}, P_{ex_C}, P_{ex_D}, P_{ex_E}$. Once this is done, we have the solutions for the model equations. In particular,

$$V_j(t) = \begin{cases} V_j^{(i)}(t) & \text{if } 0 \le t \le t_i \\ V_j^{(e)}(t) & \text{if } t_i \le t \le t_{tot} \end{cases} \tag{4}$$

for $j = A, B, C, D, E$.

A similar exercise can be performed in the case of volume-controlled ventilation. In this case the flow at the airway is controlled by the ventilator *i.e.,* $Q_{aw} = Q_{set}$ where Q_{set} is a fixed flow that is related to the desired tidal volume, V_T. Since there is little difference in the derivation, we do not include the details here.

3 Model Simulations

In this section we perform simulations of the model developed in the previous section. In particular, we investigate the effect of compartmental resistances (R_A, R_B, R_C, R_D, R_E), compartmental compliances (C_A, C_B, C_C, C_D, C_E), and the resistances of connecting airways (R_{LTR}, R_{LBR}, R_{RMR}) on the end-expiratory and peak compartmental pressures using the two modes of ventilation (PCV and VCV) with both types of ventilation delivering the *same* tidal volume over one breath. We attempt to show that for certain combinations of parameters in each class (compartmental resistances, compartmental compliances, and connecting airway resistances), volume-controlled ventilation (with $Q_{aw}(t) = Q_{set}$) produces larger peak compartmental pressures and larger variations between highest and lowest peak compartmental pressures.

The mathematical model developed in the previous section allows one to compute tidal volumes ($V_j^{(i)}(t_i) = V_{T_j}$), end-expiratory pressures (P_{ex_j}) and peak-pressures ($P_{pk_j} = V_j^{(i)}/C_j + P_{ex_j}$) for each compartment and the overall system for each mode of ventilation. In the first set of simulations, we have chosen a setup where we vary **compartmental resistances**, but we keep the compartment compliances fixed along with the resistances of the connecting airway. Each compartment has the same compliance ($C_A = C_B = C_C = C_D = C_E = 0.01\ L/cm\ H_2O$) so that the overall compliance is $C = 0.05\ L/cm\ H_2O$, and the resistances of the individual connecting airways are set as $R_{LTR} = 4\ cm\ H_2O/L/sec$, $R_{LBR} = 9\ cm\ H_2O/(L/sec)$ and $R_{RMR} = 5\ cm\ H_2O/(L/sec)$. The length of a breath was set at 2 *sec* with a duty cycle of 0.5 so that $t_i = 1\ sec$. In the pressure-controlled mode, $P_{set} = 30\ cm\ H_2O$ with a peep of 5 $cm\ H_2O$. In the volume-controlled mode, the flow was chosen to produce the same tidal volume: $V_T = 1.15314\ L$. Simulations were performed using fixed compliances and connecting airway resistances while letting the compartmental resistances vary from $5 - 15\ cm\ H_2O/L$ in increments of 5. This calculation gives 243 combinations for which we have compartmental volumes and pressures. In Figures 2-3, we illustrate one of the simulations. The resistances for the individual compartments were assigned the values: $R_A = 10$, $R_B = 10$, $R_C = 15$, $R_D = 5$ and $R_E = 5$ (all with the units $cm\ H_2O/(L/sec)$). Figure 2 shows the dynamic volumes for inspiration and expiration over one breath for the individual compartments. It is interesting to note that the volume profiles for each compartment can be quite different in appearance than the overall volume profile. In Figure 3, we compare peak pressures and end-expiratory pressures for each compartment. For PCV ($P_{aw} \equiv 30\ cm\ H_2O$), the maximum compartmental peak pressure was 29.968 and the minimum compartmental peak pressure was 27.623. For VCV with the same tidal volume, the maximum compartmental peak pressure was 34.616 and the minimum 27.432. Hence, for this relatively small range of compartmental resistances, there is a

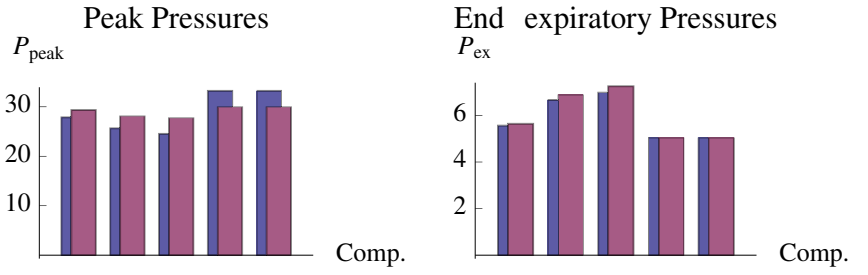

Fig. 3. Peak pressures and end-expiratory pressure for each compartment with each mode of ventilation (red-PCV, blue-VCV) for Figure 2

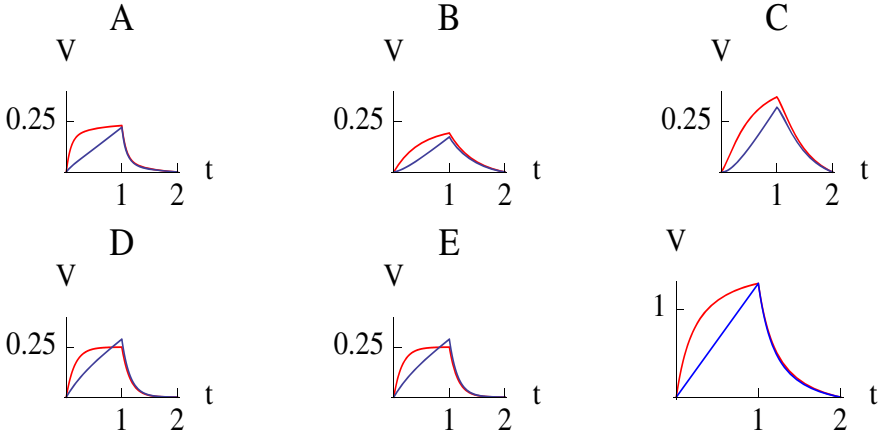

Fig. 4. Dynamic volume for each compartment for two modes of ventilation: pressure-controlled (CP-red) and volume-controlled (CF-blue). Here the compartmental resistances are 5 $cm\ H_2O$ and there is heterogeneity in the compartmental compliances: $C_A = C_B = C_D = C_E = 0.01$, $C_C = 0.02\ L/cm\ H_2O$.

difference of 4.648 $cm\ H_2O$ between the two modes of ventilation. For a clinician, having a peak pressures over 30 $cm\ H_2O$ in one of the compartments is significant.

A second set of simulations was performed where the compartmental resistances were fixed at $5/cm/H_2O/(L/sec)$ while letting the **compartmental compliances** vary between $0.01 - 0.03\ L/cm\ H_2O$. Simulations for one of these combinations are shown in Figures 4-5. In this case, the compartmental compliances were set at $C_A = C_B = C_C = C_D = C_E = 0.01\ L/cm\ H_2O$ and $C_C = 0.02\ L/cm\ H_2O$. The peak compartmental pressure for PCV was 29.97 $cm\ H_2O$ and for VCV it was 33.94 $cm\ H_2O$. As one can see from Figure 5, the end-expiratory pressures for both modes of ventilation were

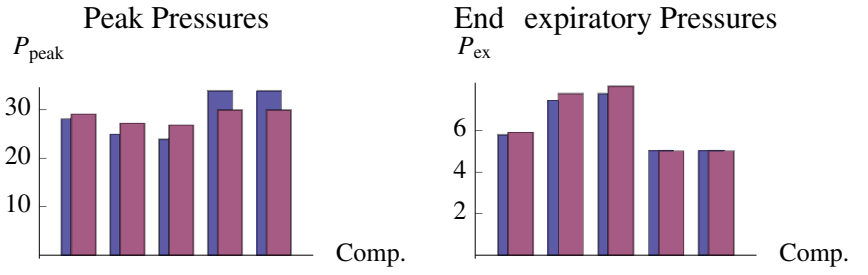

Fig. 5. Peak pressures and end-expiratory pressure for each compartment with each mode of ventilation for Figure 4

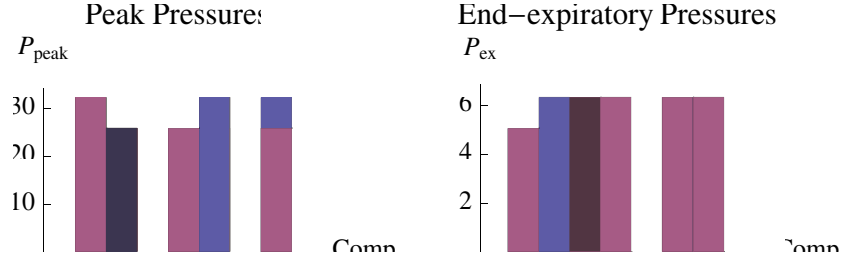

Fig. 6. Peak pressures and end-expiratory pressure for each compartment with each mode of ventilation for varying connecting airways resistances

very close and hence, the difference in peak pressures were due to dynamic effects.

A third set of simulations had the compartmental compliances set at 0.02 $L/cm\ H_2O$ and the compartmental resistances set at $5/cm/H_2O$. The **resistances for the connecting airways**, R_{LTR}, R_{LBR} and R_{RMR}, were then varied between $5-15\ cm\ H_2O/(L/sec)$. For $R_{LTR} = 5$, $R_{LBR} = 10$, and $R_{RMR} = 15$, the ratio between the maximum and minimum peak pressures was 1.04 for PCV and 1.45 for VCV. The peak pressures and end-expiratory pressures are shown in Figure 6.

In the simulations above, the PEEP was set at 5 $cm\ H_2O$. When no PEEP was used in the simulations, the differences between the smallest and largest compartmental peak pressures in VCV increased. For example in the third set of simulations, the ratio of the largest-to-smallest ratio is 1.45 in the case when $P_{PEEP} = 5$ and 1.58 when $P_{PEEP} = 0$. Hence, it appears that PEEP tends to mollify the heterogeneity effects. Comparisons in the P_{peak} and P_{ex} for the case of PEEP and no-PEEP are shown in Figure 7. When $P_{PEEP} =$ 10 $cm\ H_2O$, the ratio between the largest and smallest peak compartmental pressure was 1.34 for VCV. In Table 1, we summarize the effect of PEEP on the the maximum and minimum compartmental pressures and their ratio.

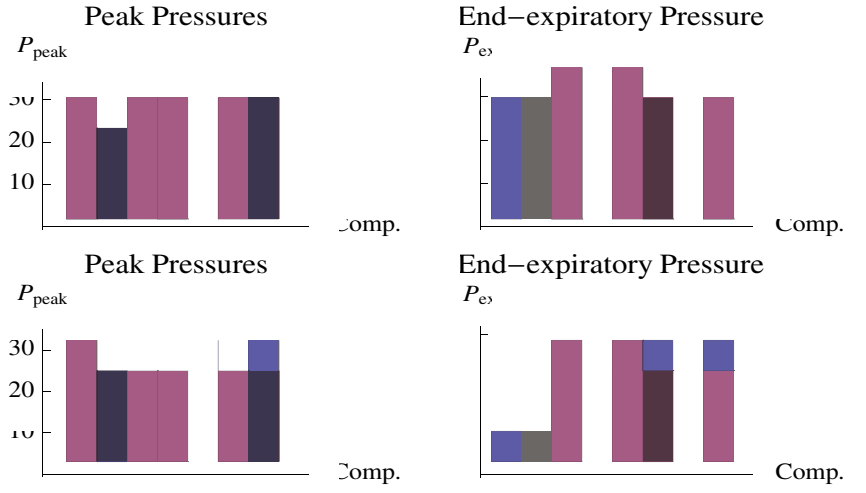

Fig. 7. Comparison of peak compartmental and end-expiratory pressures with (top) and without (bottom) PEEP

Table 1. The effect of PEEP on max. and min. peak compartmental pressures in VCV case

PEEP	Max-Min Ratio	Max P_{peak}	Min P_{peak}
0	1.58	34.36	21.25
2.5	1.52	34.00	22.43
5.0	1.45	33.64	23.12
7.5	1.39	33.27	23.81
10.0	1.34	32.91	24.50
12.5	1.29	32.55	25.18
15.0	1.24	32.18	25.87

Besides VCV and PCV, decelerating flow ventilation is often employed in the ICU. In this mode of ventilation, a controlled flow is given at the airway opening during inspiration. In particular, if $Q_{aw}(t)$ denotes the airway opening flow, then $Q_{aw}(t) = \alpha - \beta t$ where α and β are positive constants. We use our mathematical model to compare decelerating flow ventilation (DFV) against VCV (with $Q_{aw}(t) = Q_{set}$) in the five compartment system. Keeping the same inspiratory time and requiring $Q_{aw}(t_i) = 0$, we choose $\alpha = V_T/t_i$ and $\beta = V_T/t_i^2$. Using different combinations of compartmental compliances, compartmental resistances, and connecting airway resistances we studied the peak compartmental pressure and the ratio between the highest and lowest peak compartmental pressures. From these studies (by varying the impedance parameters of the compartments over clinically relevant ranges),

it appears that DFV counteracts the effects of variation in the impedance characteristics.

In DFV, the clinician has the choice of the initial flow. The choice of this initial flow is often a multiple of the desired minute ventilation which we term, *minute ventilation factor* ($\dot{V}_E$ *factor*). We investigated the effects of the the minute ventilation factor on variation of the peak compartmental pressures. To illustrate this effect, we set the compartmental resistances set at 5 $cm\ H_2O/(L/sec)$, $R_{LTR} = R_{LBR} = 5\ cm\ H_2O(/L/sec)$, and $R_{RMR} = 10\ cm\ H_2O/L/sec$ and varied the minute ventilation factor. These computations are summarized in Figure 8. It appears that the largest compartmental peak pressure is minimized when $\dot{V}_E\ factor = 4$. This is in agreement with the ventilator management standard that the initial flow in DFV should be approximately 5 times the desired minute ventilation.

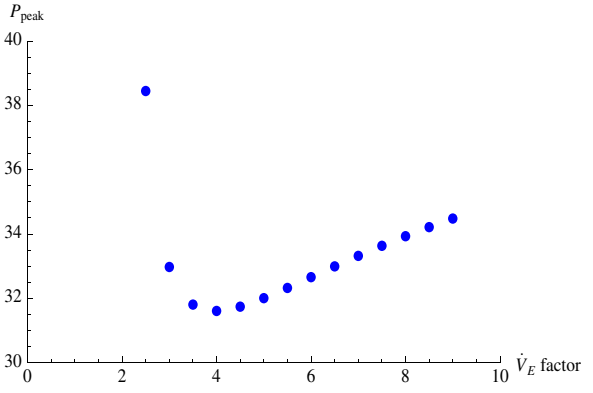

Fig. 8. Peak compartmental pressure as a function of minute ventilation factor

It is relatively easy to add compartments to the model and to change the topology of the network (*e.g.,* a three branch network). However, the present setup for the model illustrates that differences exists between the two basic modes of ventilation.

4 Discussion

Our results demonstrate that, at a fixed tidal volume and in the presence of compartmental heterogeneity, the following observations can be made from the model:

- There can be substantial heterogeneity in peak compartmental pressures on the order of several centimeters of water during both pressure control (PCV) and volume controlled ventilation (VCV);

- The peak compartmental pressure never exceeded the set airway opening pressure during pressure control ventilation (30 $cm\ H_2O$). In contrast, during VCV at the same tidal volume, peak compartmental pressures could be as high as 35 $cm\ H_2O$;
- The degree of heterogeneity in peak compartmental pressures was lower with PCV than with VCV;
- The addition of positive end expiratory pressure (PEEP) attenuates the heterogeneity of peak strain during VCV;
- There is sequential filling of compartments in volume VCV, as some compartments fill progressively more rapidly during inspiration, whereas during PCV flow into all compartments falls during inflation.

The heterogeneity of peak compartmental pressures, and presumably strains, would not be evident under current clinical monitoring approaches (primarily the measurement of peak pressure). Accordingly, clinical protocols or trials predicated on limiting tidal volume and/or monitoring peak pressures would not detect regional overdistention. Importantly, the magnitude of the differences is clinically relevant: in VCV, the peak compartmental pressures could be well above those targeted in the ARDSNet trial, despite a peak pressure that was of acceptable magnitude. These findings could, in part, explain the inability of Brower *et al.* [5] to identify a safe peak pressure (or a breakpoint in mortality at a specific level of peak pressure) during volume cycled ventilation. Because peak pressure is a global measure obtained after an end inspiratory pause, regional overdistention can be present even at a low peak pressure. Accordingly, particularly during VCV, ventilation at acceptable peak pressures could be accompanied by regional overdistention of a potentially injurious magnitude, triggering focal lung injury, increased regional permeability, and cytokine release. It is intriguing to speculate that such processes could promote more diffuse lung injury either via release of proinflammatory mediators, or by reducing the compliance of the most severely overstressed lung region and consequently increasing the stress on other, more remote, regions. Lung injury could thus progress considerably before being reflected in a clinically detectable change in peak pressure or compliance.

In contrast to the situation during VCV, the peak distending pressures during PCV never exceed the pressure at the airway opening. Accordingly, if P_{aw} is limited to less than 30 $cm\ H_2O$, no compartment will experience a peak stress greater than this value. As PCV has been shown to produce the same tidal volumes at lower set airway pressures than VCV ([13]), this suggests that it may have less potential for regional overdistention. Moreover, if impedance characteristics are changing (for example, due to mucous plugging, progressive edema formation, bronchospasm, or pleural processes), PCV ensures that no compartment will be even transiently exposed to unacceptable distending pressures, as long as adequate inspiratory times are ensured. These benefits must be weighed against the potential for greater shearing forces due to more rapid compartmental filling.

In this model, applied PEEP reduced heterogeneity of peak compartmental pressures during VCV, most likely as a result of modulating expiratory dynamics. The effect was less marked in PCV, where compartmental pressure gradients play a larger role in setting total initial inspiratory flow. This suggests that the application of PEEP, even in a linear system, might have salutary effects on the distribution of peak stresses and the accompanying strains. Notably, studies demonstrating no benefit of PEEP in ARDS have titrated this parameter based on oxygenation and FIO_2; our results suggest that there might be a mechanics-related benefit even in the absence of recruitment/derecruitment. Our model did not incorporate impedance characteristics (*e.g.*, C_j is a function of V_j) that change during the respiratory cycle (such as recruitment/derecruitment of lung regions). It seems likely that the lack of flow limitation during PCV (promoting more rapid inspiratory filling) would aid in recruitment; however, this is at present an unproven hypothesis. Moreover, although Chellboina *et al.* [18] have elegantly demonstrated that linear multicompartment models are dynamically stable, such stability might not obtain in multicompartment models having nonlinear compartmental impedance characteristics. The extent to which the benefits of PCV could be obtained by applying a linearly decelerating flow pattern is also not certain. Our preliminary work in this area suggests that decelerating flow VCV attenuates but does not eliminate compartmental heterogeneity, and PCV still results in less regional overdistention. Nonetheless, the advantages of PCV in the setting of unstable impedance characteristics remain.

5 Conclusions

Our results indicate that there can be substantial heterogeneity of peak compartmental pressures during VCV, and that this heterogeneity can be of a clinically relevant magnitude. PCV is accompanied by less regional heterogeneity and lower maximal compartmental distending pressures. Even with modest airway flows, there can be substantial regional overpressure during VCV. More detailed analyses, encompassing biological validation, techniques for detecting overdistention from airway opening flow/pressure tracings ([20–22]), and other flow patterns are warranted.

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