The Pressure–Volume Curve Is Greatly Modified by Recruitment

A Mathematical Model of ARDS Lungs

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A mathematical model of the ARDS lung, with simulated gravitational superimposed pressure, evaluated the effect of varying alveolar threshold opening pressures (TOP), PEEP and peak inspiratory pressure (PIP) on the static pressure–volume (PV) curve. The lower inflection point (Pflex) was affected by SP and TOP, and did not accurately indicate PEEP required to prevent end-expiratory collapse. Reinflation of collapsed lung units (recruitment) continued on the linear portion of the PV curve, which had a slope at any volume greater than the total compliance of aerated alveoli. As recruitment diminished, the reduced PV slope could produce an upper Pflex at 20 to 30 cm H_2O pressure. An upper Pflex caused by alveolar overdistension could be modified or eliminated by recruitment with high TOP. With constant PIP as PEEP increased, and TOP range of 5 to 60 cm H_2O, PEEP to prevent end-expiratory collapse was indicated by minimum PV slope above 20 cm H_2O, minimum hysteresis, and maximum volume at a pressure of 20 cm H_2O. With constant inflation volume as PEEP increased, the effect on PV slope was unpredictable. Although increased PV slope indicated recruitment, maximum PV slope usually underestimated PEEP required to prevent end-expiratory collapse. Therefore, with this model the PV curve did not reliably predict optimal ventilator settings. Hickling KG. The pressure–volume curve is greatly modified by recruitment: a mathematical model of ARDS lungs.

AM J RESPIR CRIT CARE MED 1998;158:194–202.

Animal studies have shown that mechanical ventilation can produce acute parenchymal lung injury and an inflammatory response (1–4) either when the lung is overdistended or when ventilation occurs with a low end-expiratory lung volume in surfactant-depleted lungs, allowing repeated end-expiratory collapse and tidal reinflation (2–4). In saline-lavaged lungs, setting the level of positive end-expiratory pressure (PEEP) higher than the lower inflection point (Pflex) of the respiratory pressure–volume (PV) curve almost entirely prevents the latter type of injury, provided that end-inspiratory lung overdistension is avoided (2, 3); this protective effect of PEEP is thought to be due to the maintenance of a higher end-expiratory lung volume and prevention of end-expiratory collapse (3). It has been suggested that setting PEEP above the lower Pflex may be beneficial in patients with adult respiratory distress syndrome (ARDS), and a randomized trial of a modified ventilatory strategy incorporating this approach as well as permissive hypercapnia showed a reduced mortality rate (5) and reduced barotrauma (6). It is difficult to measure absolute lung volume at the bedside in ventilated patients, so the prevention of end-expiratory collapse with PEEP (resulting in a higher volume at equivalent pressure during inflation) cannot easily be determined. Therefore, in patients with ARDS, the PEEP level required to prevent end-expiratory collapse is often estimated from changes in PV slope as PEEP is increased, or from the lower inflection point or zone (Pflex) of the PV curve measured from ambient pressure.

However, it is not clear whether this is the optimal approach to setting PEEP in ARDS. It has been suggested the lower Pflex of the PV curve represents the range over which aeration of previously collapsed lung (recruitment) occurs. It was suggested that no further recruitment should occur on the linear portion above the lower Pflex because if more recruitment occurs the PV slope should increase and the curve should have an upwards concavity. Therefore, if ventilation is conducted over the linear portion of the PV curve between the lower and upper Pflex, this should prevent both end-expiratory collapse and end-inspiratory overdistension, and should minimize ventilator-induced injury (7). Furthermore, it has recently been reported that some patients with ARDS show an upper Pflex at pressures as low as 20 cm H_2O (8), and it was suggested that the plateau pressure during mechanical ventilation should be limited to the pressure at the upper Pflex in such patients in order to avoid lung overdistension.

However, these assumptions about the significance of the lower Pflex, the linear portion of the PV curve, and the upper Pflex when it occurs at low pressures may be incorrect. During inflation of excised saline-lavaged rabbit lungs, recruitment of previously collapsed lung appears to continue well above the lower Pflex (K. Hickling, unpublished observations). Data from a recent CT scan study of patients with ARDS also showed

(*Received in original form August 12, 1997 and in revised form March 5, 1998*)

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Am J Respir Crit Care Med Vol 158. pp 194–202, 1998
Internet address: www.atsjournals.org

that end-inspiratory aeration of the lowermost lung regions increased as plateau pressure was increased up to a mean of 46 cm H_2O (9). Higher levels of plateau pressure were not studied, so it is possible that greater aeration may have occurred at even higher pressures. A study of saline-lavaged pigs showed that 10 min of ventilation with a plateau pressure of 55 cm H_2O was required to achieve full aeration of the lungs on CT scan after previous collapse, whereas aeration could be maintained after this with lower levels of peak and mean airway pressure (10). This is not at all surprising because it is well known that alveoli or small airways require a much higher pressure to reinflate them once collapsed than that required to maintain inflation, especially in surfactant-depleted lungs (11), as expected from Laplace's law. Laplace's law states that the pressure generated within a spherical bubble by surface tension forces is equal to 4t/r, where t is the surface tension and r the radius of the sphere. The air-liquid interface in the small airway proximal to a collapsed alveolus has a very small radius of curvature, so a high pressure is required (the "opening pressure") to advance this interface and inflate the alveolus, especially in surfactant depleted lungs. Once the alveolus is inflated to a normal or high volume, the radius of curvature is much larger, and so the pressure required to overcome surface tension forces is much less. In surfactant-depleted lungs, the lower Pflex would be expected to reflect mainly the opening pressures of lung units, and the pressure required to maintain aeration during deflation should theoretically be indicated more by the deflation limb of the PV curve. It has been suggested that the main effect of PEEP in ARDS is to oppose the superimposed pressure resulting from the weight of the overlying lung (12), and this may not be closely related to the lower Pflex. Only if the pressures required to overcome surface tension forces were zero for all lung units would the lower Pflex be expected to reflect the superimposed pressure.

In order to facilitate an understanding of the shape of the PV curve in ARDS, a simple mathematical model was constructed. The model was used to evaluate the effect of varying alveolar opening pressures and PEEP on the slope of the PV curve between the upper and lower Pflex, the pressures at the upper and lower Pflex, and the relationship between the upper and lower Pflex and ideal ventilator settings.

METHODS

Definitions and Abbreviations Used for the Model

Airway pressure. Simulated pressure in the airway and alveoli during static no-flow conditions. *Superimposed pressure (SP).* A simulation of the gravitationally determined superimposed pressure in each lung compartment; in the model this is subtracted from the airway pressure to obtain the transalveolar pressure. *Transalveolar pressure (Pta).* Airway pressure minus superimposed pressure. *Peak inspiratory pressure (PIP).* The maximum static pressure reached during measurement of the PV curve, and also during previous cycling ("ventilation") of the lung (i.e., the end-inspiratory plateau pressure during ventilation). *PEEP.* The minimum pressure reached during measurement of the PV curve and also during previous cycling of the lung. *Optimum PEEP.* The minimum end-expiratory pressure required to prevent any end-expiratory collapse of alveoli that are aerated at end-inspiration. *Threshold opening pressure (TOP).* A transalveolar pressure that must be exceeded before a lung unit can increase its volume above zero, once it has collapsed. *Lower inflection point (lower Pflex).* A region of increasing PV slope usually occurring between pressures of 0 and 20 cm H_2O. *Upper inflection point (upper Pflex).* A region of decreasing PV slope, usually occurring between pressures of 15 and 40 cm H_2O. *Pressure Volume (PV) slope.* The slope (dV/dP) of the PV curve at any point. *Mean tidal PV slope.* The mean PV slope from beginning to end of inspiration. *Recruitment.* Aeration during inflation of alveoli that were previously collapsed. *End-expiratory recruitment.* An increase in the number of aerated alveoli at end expiration after an increase in PEEP or PIP. *End-inspiratory recruitment.* An increase in the number of aerated alveoli at end-inspiration after a change in PEEP or PIP. *Tidal recruitment.* Repeated aeration of lung units during inflation, which collapse again during deflation. *Total alveolar compliance.* The volume increment produced by a 1 cm H_2O pressure increment in alveoli that were aerated prior to the pressure increment. This definition excludes any volume increment contributed by alveoli that were collapsed initially but were recruited when their TOP was exceeded after the pressure increment. In the model, when such alveoli are recruited, their volume immediately increases from zero to the appropriate volume at the new transalveolar pressure, so that their volume increase is much greater than that of alveoli that were inflated before the pressure increment. *See* Figure 2, *left panel,* and the related text for further clarification of this term.

The Model

The program was written in Qbasic. The program and various modifications are shown in the Appendix. The lung was modeled as 27,000

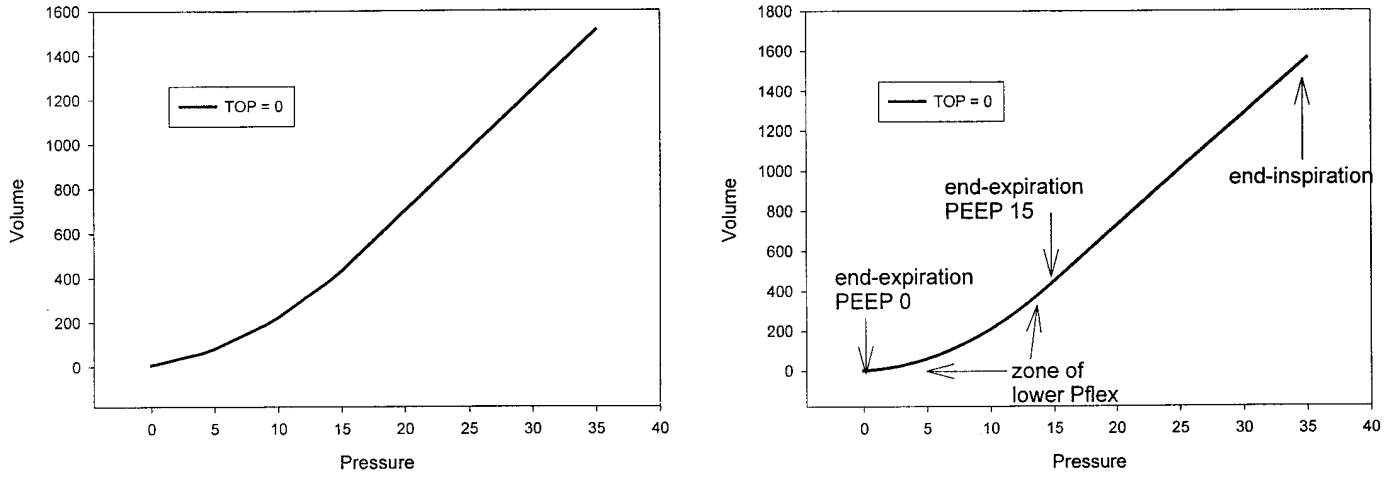


Figure 1. (*Left panel*) Pressure–volume (PV) plot of the four compartment model, consisting of 4 linear segments. TOP = threshold opening pressure. The slope increases as each compartment is recruited when the airway pressure exceeds the superimposed pressure. (*Right panel*) PV plot of the 30 compartment model. TOP = threshold opening pressure. The lower inflection point (Pflex) is a smooth curve. PEEP shifts the end-expiratory point upwards on the same PV plot as indicated.

"alveoli"; these could be assigned either linear compliance (initial simulations, Figures 1 to 3), or compliance progressively decreasing at pressure > 25 cm H_2O (later simulations, Figures 4 to 6). For these later simulations, the function $Vmod = 2V - 0.12V^{1.7}$ (where Vmod is the modified alveolar volume) was used to modify the alveolar volume at increasing pressure, simulating the upper inflection point seen at high volumes in normal lungs. The model had multiple compartments representing horizontal "slices" of lung, with increasing gravitational superimposed pressure in each compartment from 0 in the uppermost (nondependent) to 15 cm H_2O in the lowermost (dependent), according to the model of Gattinoni and colleagues (12). Simulations were performed with four compartments (Figures 1, *left panel*, and 2, *left panel*) or 30 compartments (all other simulations). The gravitational superimposed pressure was modeled as a constant pressure for each compartment, which was subtracted from the variable airway pressure to derive the transalveolar pressure. Alveolar volume was zero when transalveolar pressure was zero or negative, and it increased according to the alveolar compliance at positive transalveolar pressures providing that the requirements regarding threshold opening pressure were satisfied (*see below*).

Threshold opening pressures (TOP) could be entered as variables (as a single value or a range of values) to simulate alveolar or small airway opening after collapse. In the simulations shown in the figures, the TOP were uniformly distributed (an equal number of alveoli with each value of TOP) when a range of TOP was entered, although other distributions were examined. The TOP were modeled such that if an alveolus collapsed at end-expiration (transalveolar pressure ≤ 0), its volume remained zero during inflation until the transalveolar pressure exceeded the TOP. The alveolar volume then increased according to the alveolar compliance and was no longer affected by the TOP during the remainder of the inflation. When TOP for any alveolus exceeded the maximum (end-inspiratory) transalveolar pressure achieved with the airway pressure range studied, the alveolus remained collapsed throughout the respiratory cycle (i.e., the model assumed that all alveoli were collapsed prior to the initiation of the assigned PEEP and PIP values). PEEP was modeled by allowing any alveolus that was inflated at end-inspiration (transalveolar pressure > TOP) to remain inflated at end-expiration if transalveolar pressure > 0. Thus in this model, PEEP was only required to exceed the superimposed pressure to prevent end-expiratory collapse in any lung compartment, as suggested by Gattinoni and colleagues (12), and surface tension forces were ignored. The model assumed that the lung had been repeatedly cycled between the pressures entered as the PIP and PEEP, as would occur during mechanical ventilation, and that the PV curve was then measured over the same static pressure range. Each simulation generated a series of increasing airway pressures simulating inflation, and then decreasing pressures simulating deflation.

Input variables for the model were PIP, PEEP, and TOP (single value or range). The alveolar compliance and the number of compartments were predetermined in each simulation, but they could be varied between simulations.

RESULTS

Simulations with Linear Alveolar Pressure–Volume Relationship

The PV plot with four lung compartments (with SP = 0, 5, 10, and 15 cm H_2O from uppermost to lowermost compartment), linear alveolar compliance, and TOP = 0 is shown in Figure 1, left panel. During inflation from 0 to 5 cm H_2O airway pressure, only the uppermost compartment (SP = 0) is aerated, resulting in a low PV slope. During inflation from 5 to 10 cm H_2O, two compartments are aerated and the PV slope increases, from 10 to 15 cm H_2O it increases further, and above 15 cm H_2O the PV slope remains constant, as expected. Thus the plot has four linear segments. With the 30 compartment model (TOP = 0), the changes of PV slope are smoothed out, resulting in a curve up to a pressure of 15 cm H_2O, as shown in Figure 1, *right panel*. With this model, inspiration and expiration coincide on the same PV plot and the lower Pflex does indeed represent the region over which lung recruitment occurs, PEEP set above the lower Pflex does prevent end-expiratory collapse, and no recruitment occurs on the linear portion of the PV curve. The effect of PEEP is simply to move the end-expiratory point farther up the same PV curve, as shown in Figure 1, *right panel*.

The effect of adding a single TOP for all alveoli of either 6 or 12 cm H_2O is shown in Figure 2. In Figure 2, *left panel* (four lung compartments), with TOP = 12, there is no increase in volume until the airway pressure reaches 12 cm H_2O (Point a). There is then an incremental increase in volume as the uppermost compartment snaps open and increases (the steep portion between Point a and Segment 1) to its resting volume at a pressure of 12 cm H_2O. The volume then increases with in-

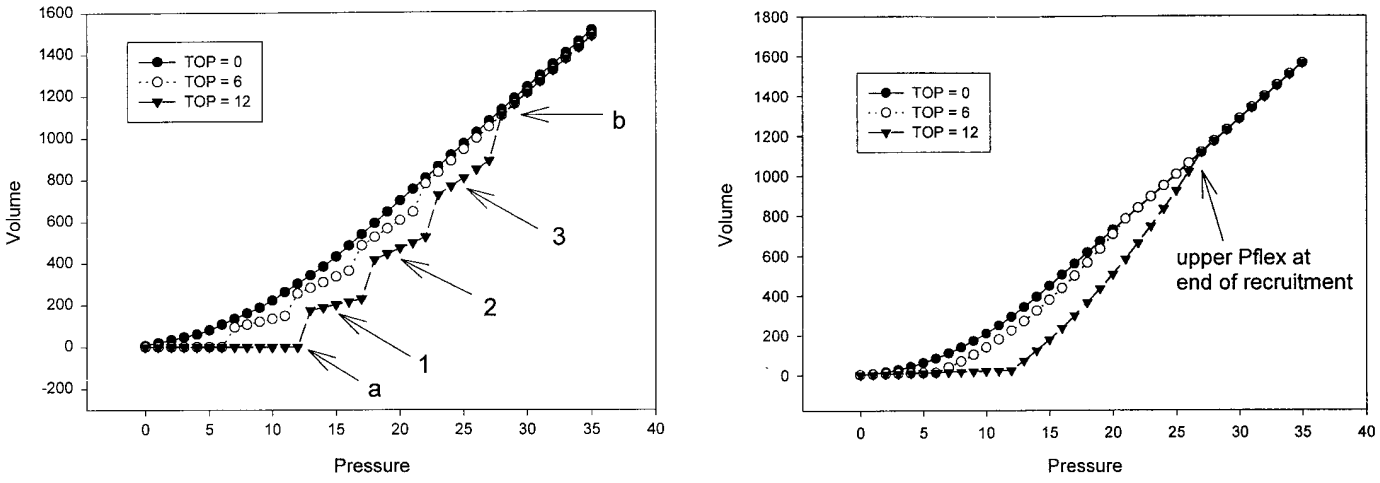


Figure 2. (*Left panel*) PV plot with opening pressures of 0, 6, and 12 cm H_2O: four compartment model. TOP = threshold opening pressure. Points a and b indicate the steep portion of the inflation PV plot, with TOP = 12, on which recruitment occurs. The slopes of the segments marked 1, 2, and 3, and above Point b, show the increasing total alveolar compliance as the compartments are recruited sequentially. Above Point b, all alveoli are aerated, and the slope therefore indicates the total alveolar compliance for all alveoli. The four steeper segments between Segments 1, 2, and 3, below Segment 1 and above Segment 3, represent the incremental volume increases that occur at the time each new compartment is recruited. (*Right panel*) PV plot with opening pressures of 0, 6, and 12 cm H_2O: 30 compartment model. TOP = threshold opening pressure. Upper Pflex = upper inflection point.

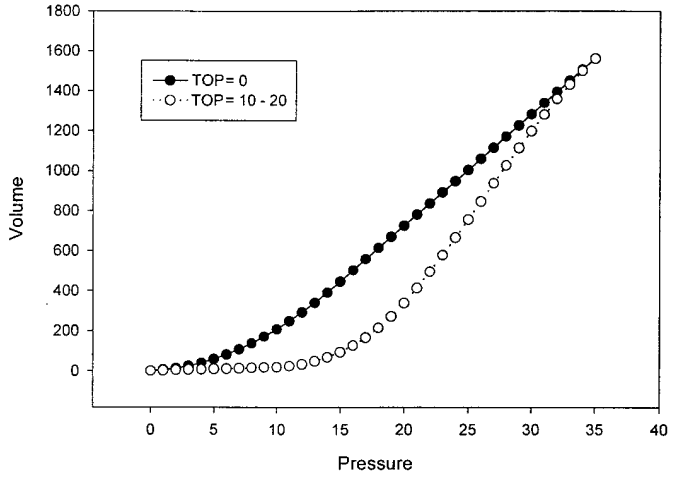


Figure 3. PV plot with range of opening pressures from 10 to 20 cm H_2O. TOP = threshold opening pressure.

creasing pressure according to the total alveolar compliance of the uppermost compartment (Segment 1), i.e., the sum of the compliances of alveoli in that compartment. When the airway pressure reaches 17 cm H_2O (12 cm H_2O above the SP of the second compartment), this in turn snaps open and immediately increases (the steep portion between Segments 1 and 2) to its volume at that transalveolar pressure (airway pressure − SP). With further pressure increases, the volume increases according to the total alveolar compliance of the two uppermost compartments (Segment 2). This continues until at a pressure of 27 cm H_2O the lowermost compartment snaps open giving a further incremental volume increase, after which the PV plot becomes linear (above Point b) and is superimposed on that of the PV curve with TOP = 0 because all lung units are aerated. Thus it is apparent that in this model, the slope of the steep portion the PV curve (between Points a and b, Figure 2, *left panel*) has two components; the increasing total alveolar compliance after each compartment is recruited (shown by the increasing slope of Segments 1, 2, and 3 and the plot above Point b), and the incremental volume increases as each compartment snaps open (i.e., recruitment; the steeper segments below Segment 1, above Segment 3, and between Segments 1, 2, and 3). If the TOP of 6 or 12 cm H_2O is added to the multiple compartment model (Figure 2, *right panel*), the incremental volume increases and increasing total alveolar compliance are smoothed out to produce a curve with upwards concavity, which has a slope at any lung volume greater than the total alveolar compliance because of recruitment. The steepest portion (just below the upper Pflex indicated in Figure 2, *right panel*) has a slope greater than the total alveolar compliance for all alveoli; when full recruitment has occurred, the PV slope suddenly reduces to that of the total alveolar compliance for all alveoli, producing an upper Pflex that is not related to alveolar overdistension (Figure 2, *right panel*). Above this pressure, the plot is superimposed on that with TOP of 0 because all alveoli are aerated. The pressure at which the upper Pflex occurs depends on both the SP and the TOP (data not shown). This upper Pflex represents the end of recruitment, and in this example it is unrelated to lung overdistension. It can also be seen that the lower Pflex is determined by TOP as well as the SP. Only the SP determines the lower Pflex for the graph with TOP = 0.

The effect of entering a range of TOP from 10 to 20 cm H_2O rather than a single value (as in Figure 2) is shown in Fig-

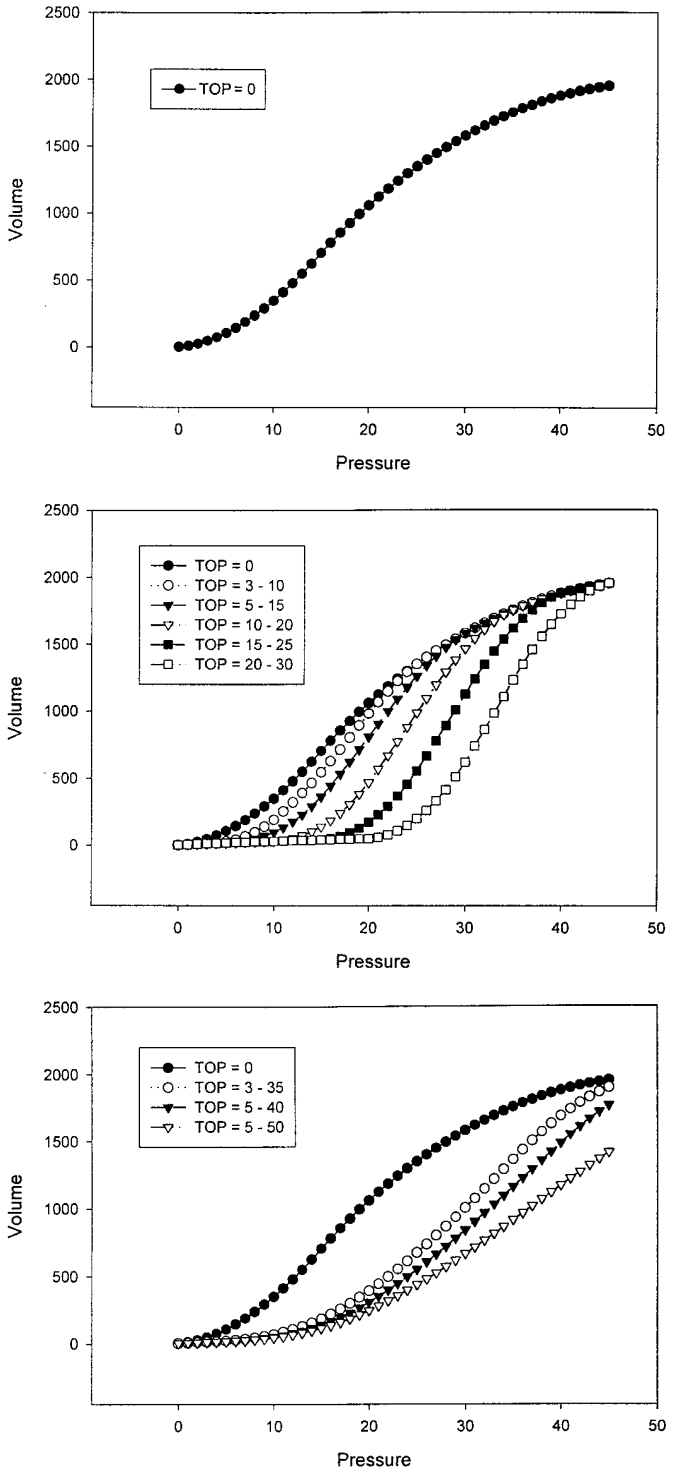


Figure 4. (*Top panel*) Upper inflection point (Pflex) programmed into alveolar compliance curve: Threshold opening pressure (TOP) = 0. (*Middle panel*) Upper inflection point (Pflex) programmed into alveolar compliance curve: PV plots are shown with threshold opening pressure (TOP) of zero and ranges from 3 to 10, 5 to 15, 10 to 20, 15 to 25, and 20 to 30 cm H_2O. (*Bottom panel*) Upper inflection point (Pflex) programmed into alveolar compliance curve: PV plots are shown with threshold opening pressure (TOP) of zero and 3 to 35, 5 to 40, 5 to 50 cm H_2O. The higher ranges of TOP mask the upper Pflex.

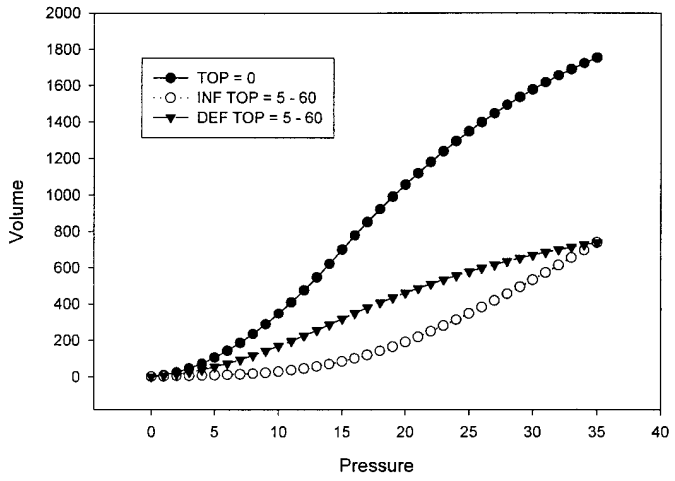


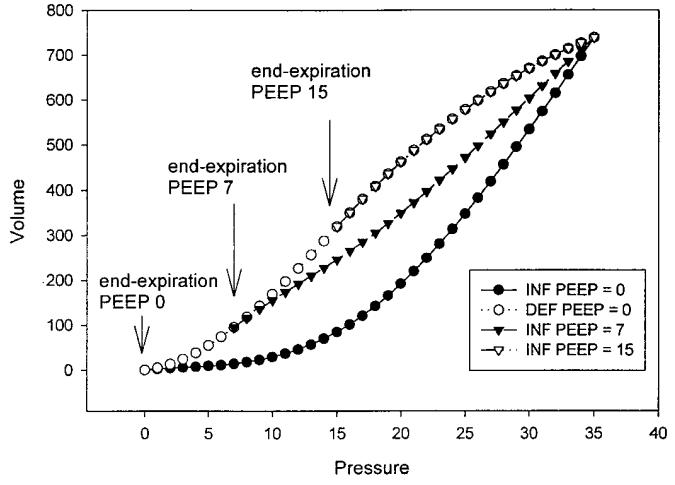
Figure 5. Effect of a range of threshold opening pressure (TOP) extended to include high pressures (5 to 60 cm H_2O). The PV curve with TOP = 0 is shown for comparison. With TOP 5 to 60 cm H_2O the lung is not fully recruited at end-inspiration (*see text*). INF = inflation; DEF = deflation.

ure 3. This has the effect of smoothing out the lower and upper Pflex, so that they become smooth curves. The region above the lower Pflex shows less upward concavity, and there is a linear portion between the upper and lower Pflex, although recruitment continues on this segment. The linear segment occurs when the increasing total alveolar compliance resulting from an increasing amount of aerated lung is matched by a decreasing rate of recruitment, which occurs after the uppermost lung level is fully recruited. When recruitment is complete, the slope again reduces to that of the graph with TOP = 0, as in Figure 2.

Simulations Using Upper Pflex Programmed into the Model

Figure 4, *top panel*, shows the PV plot using the modified program with decreasing compliance of each alveolus at pressures > 25 cm H_2O, simulating the upper Pflex seen in normal lungs. In this figure, the TOP is zero. The effect of various ranges of TOP, demonstrating that both upper and lower Pflex can be modified greatly by the TOP is shown in Figure 4, *middle panel*. With low opening pressure ranges, the pressure at which the Pflex occurs is reduced, whereas with higher ranges it is increased. The lowest TOP in the range mainly affects the lower Pflex, and the highest TOP mainly affects the upper Pflex. It can be seen in Figure 4, *bottom panel*, that ranges of TOP extending to higher values can almost completely mask the upper Pflex. Thus in this model, the upper and lower Pflex can be substantially modified by recruitment.

If the range of TOP is increased to include pressures higher than the PIP, then full recruitment of the lung is not achieved even at end-inspiration, and the deflation PV curve is no longer superimposed on that with a TOP of 0, as shown in Figure 5. If the PIP was increased sufficiently, then the inspiratory PV curve eventually would meet that with a TOP of 0, at a pressure equal to the maximum superimposed pressure plus the maximum TOP. The effect of PEEP with a TOP range of 5 to 60 cm H_2O is shown in Figure 6. The effect depends on whether the PIP is kept constant with increasing PEEP or whether the tidal volume (end-expiratory to end-inspiratory volume) is kept constant. This is analagous to determining whether V_T or PIP is kept constant while estimating "static compliance" using an end-inspiratory pause during mechanical ventilation. The effect of PEEP with a constant PIP is shown in Figure 6, *left panel*. When PEEP ⩾ the maximum superimposed pressure (15 cm H_2O), end-expiratory collapse of alveoli that are aerated at end-inspiration does not occur (i.e., there is no tidal recruitment). The inspiratory PV curve is therefore superimposed on the deflation PV curve. The lower inflection point is also eliminated because no recruitment occurs during inflation. PEEP less than the maximum superimposed pressure results in an inspiratory curve intermediate between this and the curve with no PEEP. With increasing PEEP, the volume at a pressure of 15 cm H_2O during inflation is higher, indicating end-expiratory recruitment, and thus the slope of the inspiratory PV curve from a pressure of 15 cm H_2O to the peak pressure is lower. Optimum PEEP (defined



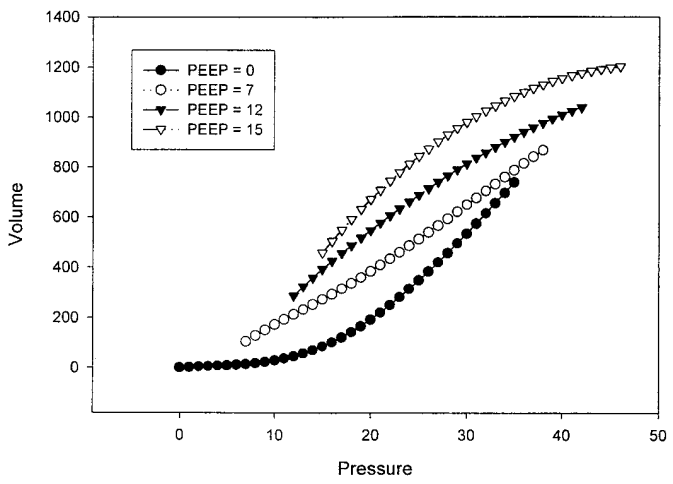


Figure 6. Effect of PEEP with high range of TOP. (*Left panel*) Constant peak inspiratory pressure: PV curves with varying PEEP and threshold opening pressure (TOP) range of 5 to 60. It is assumed that the lung has been cycled previously over the same pressure range. The volume during inflation at a pressure of 20 cm H_2O is higher as PEEP is increased, resulting in a decrease in mean PV slope. Tidal recruitment is eliminated with PEEP 15 cm H_2O, and the PV slope with PEEP 15 indicates the total alveolar compliance of alveoli that are recruited at end-inspiration with the PIP of 35 cm H_2O. (*Right panel*) Constant tidal volume: Inspiratory PV curves with varying PEEP and threshold opening pressure range of 5 to 60. It is assumed that the lung has been cycled previously over the same pressure range. End-expiratory and end-inspiratory volume are higher with higher PEEP. The change in PV slope is unpredictable (*see* DISCUSSION).

as minimum PEEP required to prevent any end-expiratory collapse of alveoli that are aerated at end-inspiration) is indicated by maximum volume at equivalent pressures during inflation, minimum hysteresis (zero in this simple model), and minimum slope of the inspiratory PV curve between the pressure of the maximum PEEP evaluated and the PIP (in this model the inspiratory curve is superimposed on the expiratory curve). If the mean tidal PV slope is measured from the end-expiratory and end-inspiratory points (as is frequently done during mechanical ventilation) there is little change in mean tidal PV slope, as indicated in Figure 6, *left panel*. If the volume of inflation is kept constant with increasing PEEP, then the end-inspiratory pressure increases and greater end-inspiratory recruitment occurs (higher volume at equivalent pressure) with increasing PEEP levels, as shown in Figure 6, *right panel*. The effect of PEEP on the PV slope depends on the relative increase in end-inspiratory and end-expiratory volume, and is less predictable than with constant PIP. However, an increase in mean tidal PV slope, indicating greater recruitment, does occur with increasing PEEP when a low V_T is used in the model to avoid end-inspiratory overdistension.

DISCUSSION

This model produces the following characteristics of the PV curve measured without PEEP:

1. The lower Pflex reflects both SP and TOP, but the latter have the greater influence. Thus the lower Pflex does not accurately predict optimum PEEP, as it does with TOP = 0 since the model assumed that PEEP > SP prevented end-expiratory collapse.
2. The linear portion of the curve is characterized by continuing recruitment, and it is steeper than the total alveolar compliance because it reflects the rate of alveolar recruitment with pressure increase as well as total alveolar compliance.
3. A decrease in PV slope can occur at the end of recruitment, or as recruitment diminishes. This decreasing rate of recruitment during inflation can create an upper Pflex at a pressure of 20 to 30 cm H_2O, which is unrelated to lung overdistension. Alternatively, depending on the range of TOP used, a decreasing rate of recruitment can decrease or increase the pressure at an upper Pflex that is caused by lung overdistension. If recruitment continues above the pressure of an upper Pflex caused by lung overdistension, the continuing recruitment can mask the upper Pflex so that it is no longer present even when alveoli are overdistended.

Effect of PEEP on PV Slope

The effect of PEEP on the PV curve depends on whether the PIP or the inflation volume is kept constant. If the PIP is kept constant as PEEP is increased, optimum PEEP to prevent end-expiratory collapse is indicated by minimum hysteresis; by maximum volume during inflation at the pressure of the maximum PEEP level, and by the minimum PV slope between the pressure of the maximum PEEP evaluated and the PIP. Increasing PEEP above optimum PEEP will cause a reduction in mean PV slope because the PV slope is reduced at higher pressures. However, with PEEP ⩾ optimum PEEP the inspiratory PV curves are all superimposed on the expiratory curve, so if they are compared between the maximum PEEP evaluated and the PIP, they are identical with PEEP levels ⩾ optimum PEEP (*see* Figure 6, *left panel*). However, if the mean tidal PV slope was estimated (i.e., only from the end-expiratory and end-inspiratory points), as is often done during mechanical ventilation, PEEP would have little effect with this model, as shown in Figure 6, *left panel*. This is partly because with PEEP = 0, this measurement includes the low PV slope portion of the curve below the lower Pflex. However, it is also a result of the fact that (*1*) the deflation limb of the PV curve in this model is the same as the inflation limb with TOP of 0, i.e., there is no inherent hysteresis in this model apart from

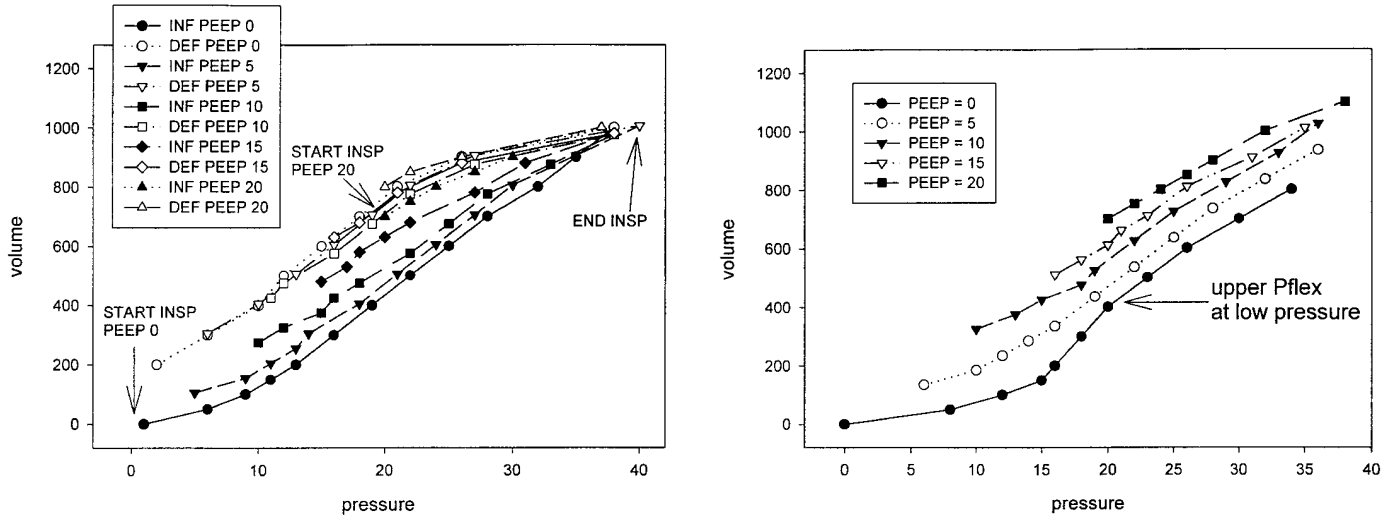


Figure 7. (*Left panel*) PV curves with constant peak pressure in a patient with ARDS. The peak pressure was maintained at the same level during ventilation at each level of PEEP between measurement of the PV curves. The end-expiratory lung volumes at each PEEP level were estimated by measuring the exhaled volume after releasing PEEP. The PV slope decreases slightly with increasing PEEP. (*Right panel*) Inspiratory PV curves with constant tidal volume in a patient with ARDS. There was little change in PV slope with increasing PEEP. The tidal volume was maintained at the same level during ventilation at each level of PEEP between measurement of the PV curves, and it was the same as the inflation volume used for the PV curve. An upper Pflex can be seen at a pressure of 20 cm H_2O, and this is not present at higher PEEP. The end-expiratory lung volumes at each PEEP level were estimated by measuring the exhaled volume after releasing PEEP.

that caused by opening pressures, and (*2*) the alveolar PV relationship during deflation is nearly linear at low volumes; there is no sudden volume reduction below a "critical closing pressure." The deflation limb of the curve therefore passes through the zero PV intercept. In reality, the deflation limb of the PV curve in ARDS has a low slope initially with decreasing pressure, and then the slope increases as pressure is reduced further (probably representing lung de-recruitment), as shown in Figure 7, *left panel.* Thus in patients with ARDS, when hysteresis is reduced with increasing PEEP, the inflation curve approximates the deflation curve, and PV slope may decrease with optimum PEEP (when PIP is constant) even when estimated only from the end-expiratory and end-inspiratory points (Figure 7, *left panel*). However, a more accurate assessment can be obtained from a complete PV curve at each level of PEEP.

When inflation volume is kept constant in the model, the change in mean tidal PV slope with increasing PEEP is variable and depends on the range and distribution of TOP, the tidal volume, and the compliance characteristics of alveoli in the model, especially the threshold for significant departure from elastic behavior. Thus the change in slope is not easily predictable. Overdistension of some alveoli, or reduced tidal recruitment as PEEP is increased, will each contribute to a decrease in the mean tidal PV slope, whereas increased end-inspiratory recruitment or increased tidal recruitment with increasing PEEP will each contribute to an increase of the mean tidal PV slope. If tidal recruitment diminishes with increasing PEEP (because of decreased end-expiratory collapse), this will oppose the effect on mean tidal PV slope of increased end-inspiratory recruitment. An increase in mean tidal PV slope with increased PEEP therefore indicates recruitment, but it is not possible to determine whether this is an increase of aerated lung throughout the ventilatory cycle, or increased tidal recruitment, or both. Increased tidal recruitment could theoretically increase ventilator-induced injury. Conversely, no change or even a decrease in mean tidal PV slope with increased PEEP could result from additional end-expiratory recruitment even if there is also a small increase in end-inspiratory recruitment (but with decreased tidal recruitment). In fact, with incomplete end-inspiratory recruitment, evaluating the effect of increments of PEEP on PV slope with a constant V_T is really testing the recruiting ability of the PIP rather than the ability of PEEP to prevent end-expiratory collapse. For example, if a very low V_T is used, an increment of PEEP above optimum PEEP may cause an increase in mean tidal PV slope because of increased end-inspiratory recruitment, even though end-expiratory collapse of the newly recruited alveoli could have been prevented by a lower level of PEEP. For any degree of end-inspiratory recruitment achieved by the increased PIP, the PV slope will actually be greater if the newly recruited alveoli collapse again at end expiration (causing more tidal recruitment), resulting in a decreased end-expiratory volume.

Inspiratory PV curves at different PEEP levels with constant inflation volume in one patient with ARDS are presented in Figure 7, *right panel,* showing that additional end-inspiratory recruitment occurred and that there was little change in mean tidal PV slope. It also shows an upper Pflex at a pressure of approximately 20 cm H_2O on the curve with PEEP = 0, which no longer occurs at higher PEEP levels, suggesting that it may have been related to diminishing recruitment rather than to lung overdistension.

Thus the effect of PEEP on PV slope is likely to be more predictable if PIP is kept constant, and in this situation optimum PEEP is indicated by the minimum PV slope between the maximum PEEP tested and the PIP. With a constant V_T, selecting the PEEP level giving the greatest mean tidal PV slope may not achieve minimum end-expiratory collapse with this model. In a clinical study of ARDS, Ranieri and colleagues (13), using constant V_T, showed that the change in PV slope with increasing PEEP was variable, and the PV slope frequently decreased even when substantial end-expiratory recruitment occurred with PEEP. They also observed greater end-expiratory recruitment with PEEP when using a small V_T, suggesting that perhaps end-inspiratory recruitment was incomplete at low PEEP levels with a low V_T. Further clinical studies would be valuable.

In the model, the effects of PEEP on the slope and upwards displacement on the volume axis of the PV curve are due entirely to recruitment effects. However, in patients, other phenomena such as stress relaxation or surface tension changes could possibly contribute to similar effects.

Implications Concerning Specific Compliance in ARDS

Another possible implication of this model concerns the specific compliance of aerated lung in ARDS. Using CT scans in patients with ARDS, Gattinoni and colleagues (14) showed that the amount of aerated lung on CT scan at each level of PEEP correlated with the mean PV slope over a pressure range encompassing the PEEP level. It was found that the specific compliance of the aerated lung (estimated as the mean PV slope of the static PV curve from a pressure of zero to the lower Pflex, divided by the amount of aerated lung on CT scan at 5 cm H_2O PEEP) was relatively normal. It has been mainly this finding that has led to the belief that the plateau pressure in ARDS should be limited to that producing lung overdistension and lung injury in normal lungs (15). If the static PV curve in ARDS actually overestimates total alveolar compliance because of recruitment, then this estimate of specific compliance could be too high. Indeed, it is rather surprising to find that the specific compliance is normal in surfactant depleted lungs. A low specific compliance in ARDS would imply that it is safe to allow a somewhat higher level of plateau pressure during mechanical ventilation than that currently recommended without lung overdistension occurring, even when chest wall compliance is normal. It seems unlikely that this will have resulted in a large error in the estimation of specific compliance because only a little recruitment probably occurs below the lower Pflex during measurement of the PV curve. However, in the model, there is some recruitment below the midpoint of the lower Pflex.

If the conclusions from this mathematical model could be extrapolated to actual measurements of the PV curve in ARDS, they would therefore have important implications regarding both the selection of PEEP and the safe level of plateau pressure from the PV curve.

Limitations of the Model

The model is very simplistic. In reality, hysteresis results from variation of surface tension from inspiration to expiration, and from low to high lung volume, and from other factors, in addition to inspiratory recruitment. There is insufficient knowledge of the detailed mechanisms and geometry of small airway and alveolar opening after collapse in ARDS to allow accurate modeling of TOP from these basic principles (16). Both collapse and re-expansion show some time-dependence, and this could not be incorporated into this simple model. However, this model does allow an examination of the effect of different values of opening pressures and superimposed pressures on the slope and inflection points of the inspiratory curve, and on its deviation from the PV curve with a TOP of

zero. To this extent, the conclusions seem likely to have some validity and can be used to generate hypotheses. In particular, the significance of an upper Pflex occurring at a low pressure, the concept of titrating PEEP to obtain "best compliance," and the relationship between the lower Pflex and the amount of PEEP required to prevent end-expiratory collapse should perhaps be reexamined.

Rather high values of TOP were used in evaluating the effect of PEEP (as high as 60 cm H_2O). However, there is evidence that such high TOP do occur in surfactant depleted lungs as discussed earlier (9, 10). A sustained inflation with an airway pressure of 30 to 40 cm H_2O was needed to reinflate postoperative atelectasis in patients with normal lungs, using CT scans to evaluate the atelectasis (17). It has also been observed that sustained inflations with relatively high pressures are sometimes effective in improving oxygenation in ARDS (18), suggesting recruitment of lung regions with high TOP. Thus it is likely that such high TOP do occur in ARDS. However, the distribution of TOP throughout the lung in ARDS is unknown.

The PV plots generated by this model simulate an inflation produced by a pressure generator using increments of pressure. There could be differences if a volume generator were simulated. For example, in Figure 2, *left panel*, the behavior of the model when each compartment becomes aerated could follow several patterns. If all units in each compartment behaved identically, the pressure would reduce as the same total lung volume was distributed into the newly opened compartment, causing pressure "indentations" in the PV curve. Alternatively, lung units in the newly opening compartment could open sequentially with increasing volume, so that the pressure changes would be negligible, or there could be intermediate behavior. However, with multiple compartments these differences would be very small. This model was not constructed to calculate pressure in response to volume changes, and could not simulate any of these behaviors in its present form.

The compliance of the chest wall in ARDS may sometimes vary at different volumes, and in some patients a lower Pflex may result from an increase in chest wall rather than lung compliance as volume increases (19). This could further increase the difficulty in interpreting the PV curve. This model did not attempt to simulate variable chest wall compliance.

In evaluating PEEP in this model, it was assumed that PEEP is only required to overcome the superimposed pressure in any compartment to prevent end-expiratory collapse, as suggested by Gattinoni and colleagues (12). Therefore, there may be dissociation between the lower Pflex (determined mainly by the TOP) and the optimum PEEP (determined only by superimposed pressure), and optimum PEEP is not well predicted by the lower Pflex. If this modeling is not completely accurate, and perhaps some additional PEEP is required to overcome surface tension forces in some lung units, this should not have an important qualitative effect on the model or the main conclusions, but it could affect the relationship between the lower Pflex and the amount of PEEP required to prevent end-expiratory collapse. However, in this model the lower Pflex indicates only the commencement of recruitment, and only the lowest TOP, and recruitment continues to pressures much higher than the lower Pflex when the range of TOP is large. Even if there were a predictable relationship between alveolar opening and closing pressures, the lower Pflex would not indicate optimum PEEP reliably; some lung units would collapse during deflation at pressures well above the lower Pflex when a wide range of TOP was used. The relationship between lower Pflex and optimum PEEP would be affected by the range of TOP used as well as the relationship between opening and closing pressures and the superimposed pressure. Only if a single value or a narrow range of TOP were used, and the closing pressures were close to the opening pressures, would there be a predictable relationship between the lower Pflex and optimum PEEP. The model did not incorporate any simulation of small airway closure, which may act to prevent true alveolar collapse at end-expiration. However, the use of a range of TOP allows for differences in opening pressure, which could occur with small airway closure in some lung regions and true alveolar collapse in others. Theoretically, the deflation limb of the PV curve should give more information about the pressure at which airway or alveolar closure starts to occur. However, this model cannot be used to describe the deflation curve. That would require a model that incorporates the forces determining alveolar collapse during expiration, and hysteresis, including surface tension forces.

In summary, according to this model, no aspect of the PV curve measured at PEEP = 0 adequately predicts optimum ventilator settings. Setting PEEP according to the lower Pflex, and the plateau pressure according to the upper Pflex, may be very misleading in the model. The PEEP giving the highest mean tidal PV slope with a constant V_T may underestimate optimum PEEP. The best method of PEEP selection would be to measure absolute lung volume and select the PEEP level giving greatest end-expiratory recruitment (highest volume during inflation at equivalent pressure), but this is not an easily available measurement at the bedside. An approach that could be investigated clinically would be to increase PEEP with a constant PIP until the PV slope measured between the pressure of the highest PEEP level tested and the PIP reaches a minimum value. According to the model, this approach should indicate the PEEP required to prevent end-expiratory collapse of lung units that are inflated at end-inspiration, i.e., to avoid tidal recruitment. According to current evidence, this may help to minimize ventilator-induced lung injury even if full end-inspiratory recruitment is not achieved. However, if the PIP is subsequently increased, or after a recruitment maneuver such as a sustained inflation, higher PEEP may be required to maintain end-expiratory aeration of any newly recruited units, and thus to maintain any improvement in oxygenation.

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APPENDIX

The Lung Model Program

1. The basic program: inflation:

```
REM assign 270000 lung units with compliance of 0.0002 each
PRINT "enter PIP"
INPUT PIP
PRINT "enter PEEP"
INPUT peep
PRINT "enter minimum opening press"
INPUT opmin
PRINT "enter maximum opening press"
INPUT opmax
PRINT "enter data filename"
INPUT file$
OPEN file$ FOR OUTPUT AS #2
PRINT #2, PIP, peep, opmin, opmax
PRINT "pip = "; PIP, "peep = "; peep, "opmin = "; opmin, "opmax = ";
      opmax
FOR press = peep TO PIP
voltot = 0
FOR sp = −.5 TO 14.5 STEP .5    'superimposed pressure
REM 30 lung levels each with 9000 units
FOR opress = opmin TO opmax
IF press > (sp + opress) THEN
  vol = (press − sp) * 9000 * .0002 / (1 + opmax − opmin)
ELSEIF PIP > (sp + opress) AND peep > sp THEN
  vol = (press − sp) * 9000 * .0002 / (1 + opmax − opmin)
ELSE vol = 0
END IF
voltot = voltot + vol
NEXT opress
NEXT sp
voltot2 = voltot       'leaves voltot as counter
PRINT #2, press, voltot2
PRINT press, voltot2
NEXT press
```

2. Deflation:

The program was the same except for the section determining whether or not lung units were open or collapsed in each lung level, which was as follows during deflation:

```
IF press > (sp + opress) THEN
vol = (press − sp) * 9000 * .0002 / (1 + opmax − opmin)
ELSEIF PIP > (sp + opress) AND press > sp THEN
  vol = (press − sp) * 9000 * .0002 / (1 + opmax − opmin)
ELSE vol = 0
END IF
```

Program modified to incorporate an upper Pflex into the compliance curve of each lung unit. The volume of each lung unit was modified according to the following function: vol = 2 * vol − 0.12 * vol ^1.7 'vol reduced at high vols